



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>6</sup> :</b> <b>C07D 209/20, 403/12, A61K 31/405</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/14666</b> <b>(43) International Publication Date:</b> 1 June 1995 (01.06.95)
<b>(21) International Application Number:</b> PCT/US94/13596 <b>(22) International Filing Date:</b> 23 November 1994 (23.11.94) <b>(30) Priority Data:</b> 157,774 24 November 1993 (24.11.93) US <b>(60) Parent Application or Grant</b> (63) Related by Continuation US 157,774 (CIP) Filed on 24 November 1993 (24.11.93) <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CHEN, Meng, Hsin [TW/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MORRIELLO, Gregori, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). NARGUND, Ravi [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). YANG, Lihu [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(74) Common Representative:</b> MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> INDOLYL GROUP CONTAINING COMPOUNDS AND THE USE THEREOF TO PROMOTE THE RELEASE OF GROWTH HORMONE(S)  <b>(57) Abstract</b> <p>The present invention is directed to certain compounds of general structural formula (I), wherein R<sub>1</sub>, R<sub>1a</sub>, R<sub>3</sub>, R<sub>3a</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, A, W, and n are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="flex: 1;"> </div> <div style="flex: 0.1; text-align: center;"> <b>(I)</b> </div> </div>		

BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTION

INDOLYL GROUP CONTAINING COMPOUNDS AND THE USE THEREOF TO PROMOTE  
THE RELEASE OF GROWTH HORMONE(S)

5     BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein  
10     synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For  
15     example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion  
20     or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous  
25     growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a  
30     very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any

- 2 -

risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones still have low oral bioavailability. Non peptidal growth hormone secretagogues with a benzolactam structure are disclosed in U.S. Patents 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

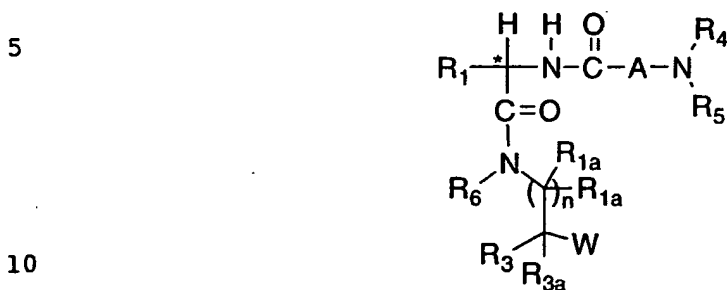
#### 15 SUMMARY OF THE INVENTION

The present invention is directed to certain compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe such compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the compounds and their analogs for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

- 3 -

DESCRIPTION OF THE INVENTION

The compounds of the present invention are best described in the following structural Formula I:



Formula I

wherein:

R<sub>1</sub> is selected from the group consisting of:

- 15 C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, (C<sub>1</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, and (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, where K is O, S(O)<sub>m</sub>, N(R<sub>2</sub>)C(O), C(O)N(R<sub>2</sub>), OC(O), C(O)O, -CR<sub>2</sub>=CR<sub>2</sub>-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindolyl,
- 20 pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where R<sub>2</sub> and alkyl may be further substituted by 1 to 9 halogen, S(O)<sub>m</sub>R<sub>2a</sub>, 1 to 3 of OR<sub>2a</sub> or C(O)OR<sub>2a</sub>, and aryl may be further substituted by 1 to 3 of C<sub>1</sub>-C<sub>6</sub> alkyl, 1 to 3 of halogen, 1 to 2 of OR<sub>2</sub>, methylenedioxy, -N(R<sub>2</sub>)(R<sub>2</sub>), -S(O)<sub>m</sub>R<sub>2</sub>, 1 to 2 of -CF<sub>3</sub>, -OCF<sub>3</sub>,
- 25 -C(O)H, nitro, -N(R<sub>2</sub>)C(O)(R<sub>2</sub>), -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -1H-tetrazol-5-yl, -SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)SO<sub>2</sub> phenyl, or -N(R<sub>2</sub>)SO<sub>2</sub>R<sub>2</sub>; R<sub>1a</sub> is independently hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and

30 C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one atom, they may be optionally joined to form a C<sub>3</sub>-C<sub>8</sub> cyclic ring, optionally including oxygen, sulfur, SO<sub>2</sub> or NR<sub>2a</sub>;

R<sub>2a</sub> is hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by hydroxyl;

- 4 -

R<sub>3</sub> is independently selected from the group consisting of:  
 hydrogen, -C<sub>1</sub>-C<sub>10</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, -(CH<sub>2</sub>)<sub>r</sub>naphthyl,  
 -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>8</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>8</sub>),  
 (C<sub>1</sub>-C<sub>6</sub> alkyl)-K-(C<sub>1</sub>-C<sub>4</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
 5 -(CH<sub>2</sub>)<sub>r</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl,  
 where K is O or S(O)<sub>m</sub>, and where heteroaryl is selected from: pyridyl,  
 indolyl, imidazolyl, quinolinyl, benzothienophenyl, benzofuranyl, indanyl,  
 thiazolyl, benzimidazolyl, and azaindolyl, and  
 where the phenyl, naphthyl and heteroaryl may be substituted by:  
 10 C<sub>1</sub>-C<sub>6</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>9</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, -C(O)H,  
 -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>2</sub>)(R<sub>9</sub>), -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>2</sub>)C(O)R<sub>9</sub>,  
 -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>9</sub>), -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>6</sub>)C(O)N(R<sub>2</sub>)(R<sub>9</sub>), or -(CH<sub>2</sub>)<sub>r</sub>(R<sub>9</sub>);

15 R<sub>3a</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>4</sub> and R<sub>5</sub> are independently selected from:  
 hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the  
 substituents are selected from: 1 to 5 halogen, 1 to 3 of hydroxy, 1 to 3  
 of C<sub>1</sub>-C<sub>10</sub> alkanoyloxy, 1 to 3 of C<sub>1</sub>-C<sub>6</sub> alkoxy, phenyl, phenoxy,  
 20 2-furyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, and S(O)<sub>m</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl); or R<sub>4</sub> and  
 R<sub>5</sub> can be taken together to form -(CH<sub>2</sub>)<sub>d</sub>L<sub>a</sub>(CH<sub>2</sub>)<sub>e</sub>- where L<sub>a</sub> is  
 C(R<sub>2</sub>)<sub>2</sub>, O, S(O)<sub>m</sub> or N(R<sub>2a</sub>), d and e are independently 1 to 3;

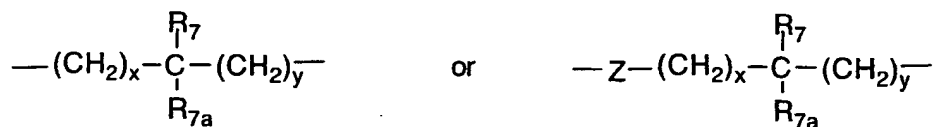
25 R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl,  
 phenyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from:  
 imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR<sub>2</sub>, S(O)<sub>m</sub>R<sub>2</sub>,  
 C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, N(R<sub>2</sub>)(R<sub>2</sub>), and  
 30 C(O)N(R<sub>2</sub>)(R<sub>2</sub>); or R<sub>7</sub> and R<sub>7a</sub> can independently be joined to one or  
 both of R<sub>4</sub> and R<sub>5</sub> groups to form an alkylene bridge between the  
 terminal nitrogen and the alkyl portion of the R<sub>7</sub> or R<sub>7a</sub> groups, wherein  
 the bridge contains 1 to 5 carbons atoms; or R<sub>7</sub> and R<sub>7a</sub> can be joined to  
 one another to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

- 5 -

- R<sub>8</sub> is selected from the group consisting of:  
 hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl  
 groups may be substituted by a substituent selected from the group  
 consisting of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
 5 and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting  
 of: phenyl, naphthyl, indolyl, quinolinyl, benzothiophenyl,  
 benzofuranyl, azaindolyl, benzimidazolyl, pyridyl, and thiazolyl, and  
 where the aryl may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen,  
 1 to 2 of C<sub>1</sub>-C<sub>3</sub> alkyl, -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), or -1H-tetrazol-5-yl;  
 10  
 R<sub>9</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or (CH<sub>2</sub>)<sub>v</sub>aryl, wherein the alkyl and  
 (CH<sub>2</sub>)<sub>v</sub> groups may be optionally substituted by 1 to 2 of -O(R<sub>2</sub>),  
 -S(O)<sub>m</sub>R<sub>2</sub>, -N(R<sub>2</sub>)(R<sub>2</sub>), 1H-tetrazol-5-yl, -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
 -SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), or -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), and where aryl is selected  
 15 from: phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl,  
 oxadiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, and benzimidazol-  
 2-yl, triazolinone-yl, and where the aryl is optionally substituted with  
 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, amino, hydroxyl, or -C(O)O(R<sub>2</sub>);

- 20 A is:



- 25 where x and y are independently 0, 1, 2 or 3;

- W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>,  
 -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)NH-SO<sub>2</sub>(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>),  
 -CH<sub>2</sub>N(R<sub>2</sub>)C(O)R<sub>8</sub>, -CH<sub>2</sub>N(R<sub>2</sub>)C(O)(R<sub>8</sub>), -(CH<sub>2</sub>)<sub>r</sub>OR<sub>2</sub>,  
 30 -CH(OH)R<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>R<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), 1H-tetrazol-5-yl,  
 5-amino-1,2,4-oxadiazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl,  
 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

- 6 -

m is 0, 1, or 2;  
n is 0 or 1;  
r is 0, 1, 2, or 3;  
v is 0, 1, or 2 ;

5 and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

10 The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl (Me), ethyl (Et), propyl (Pr), isopropyl (i-Pr), butyl (Bu), sec-butyl (s-Bu), tertiary butyl (t-Bu), pentyl, isopentyl, hexyl, isohexyl, allyl, propinyl, 15 butadienyl, hexenyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain 20 double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, propinyloxy, isobutenyloxy, hexenyloxy and the like.

25 The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, 30 indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl, quinolinyl, pyrazinyl, or isothiazolyl, which may be optionally substituted by 1 to 3 of C<sub>1</sub>-C<sub>6</sub> alkyl, 1 to 3 of halogen, 1 to 2 of -OR<sub>2</sub>, -N(R<sub>2</sub>)(R<sub>2</sub>), methylenedioxy, -S(O)<sub>m</sub>R<sub>2</sub>, 1 to 2 of -CF<sub>3</sub>, -OCF<sub>3</sub>, nitro, -N(R<sub>2</sub>)C(O)(R<sub>2</sub>), -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -1H-

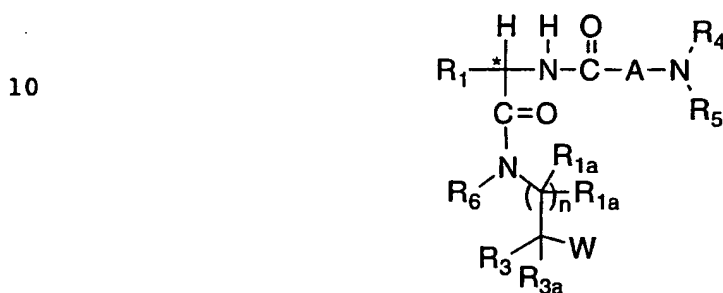


- 7 -

tetrazol-5-yl, -SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)SO<sub>2</sub> phenyl, or -N(R<sub>2</sub>)SO<sub>2</sub>R<sub>2</sub>, wherein R<sub>2</sub> is as defined herein.

Certain of the above defined terms may occur more than once in the above formula or definitions and upon such occurrence, each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:



Formula Ia

wherein:

R<sub>1</sub> is selected from the group consisting of:

20 C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, (C<sub>1</sub>-C<sub>4</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>2</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, and (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)(C<sub>0</sub>-C<sub>2</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, where K is O, S(O)<sub>m</sub>, OC(O), or C(O)O, where the alkyl groups may be further substituted by 1 to 7 halogen, S(O)<sub>m</sub>R<sub>2a</sub>, 1 to 3 of OR<sub>2a</sub> or C(O)OR<sub>2a</sub>, and where aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindolyl, benzothienyl, and benzofuranyl, and where the aryl may be further substituted by 1 to 2 of C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of halogen, -C(O)H, 1 to 2 of -OR<sub>2</sub>, -S(O)<sub>m</sub>R<sub>2</sub>, or -C(O)OR<sub>2</sub>;

R<sub>1a</sub> is independently hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

30 R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one atom they may be optionally joined to form a C<sub>4</sub>-C<sub>7</sub> cyclic ring optionally including oxygen, sulfur or NR<sub>2a</sub>;

R<sub>2a</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

- 8 -

R<sub>3</sub> is independently selected from the group consisting of:  
hydrogen, -C<sub>1</sub>-C<sub>8</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, -(CH<sub>2</sub>)<sub>r</sub>naphthyl,  
and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl, where heteroaryl is selected from: pyridyl,  
indolyl, quinoliny, benzothiophenyl, benzofuranyl, thiazolyl,  
5 benzimidazolyl, and azaindolyl, and where the phenyl, naphthyl and  
heteroaryl may be substituted by: C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of halogen, 1 to 2  
of -OR<sub>2</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>2</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
-(CH<sub>2</sub>)<sub>r</sub>N(R<sub>6</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), or -(CH<sub>2</sub>)<sub>r</sub> (R<sub>9</sub>);

10 R<sub>3a</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>4</sub> and R<sub>5</sub> are independently selected from: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and  
substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from: 1 to 5  
of halogen, 1 to 3 of hydroxyl, S(O)<sub>m</sub> (C<sub>1</sub>-C<sub>6</sub> alkyl), and phenyl;

15

R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl,  
phenyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from:  
20 imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR<sub>2</sub>, S(O)<sub>m</sub>R<sub>2</sub>,  
C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, N(R<sub>2</sub>)(R<sub>2</sub>), and  
C(O)N(R<sub>2</sub>)(R<sub>2</sub>); or R<sub>7</sub> and R<sub>7a</sub> can independently be joined to one or  
both of R<sub>4</sub> and R<sub>5</sub> groups to form an alkylene bridge between the  
terminal nitrogen and the alkyl portion of the R<sub>7</sub> or R<sub>7a</sub> groups, wherein  
25 the bridge contains 1 to 5 carbons atoms; or R<sub>7</sub> and R<sub>7a</sub> can be joined to  
one another to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

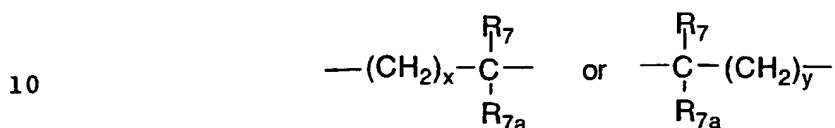
R<sub>8</sub> is selected from the group consisting of:  
hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl  
30 groups may be substituted by a substituent selected from the group  
consisting of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting  
of: phenyl, indolyl, azaindolyl, pyridyl, and thiazolyl, and where the aryl  
may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen, or 1 to 2 of

- 9 -

C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>9</sub> is (CH<sub>2</sub>)<sub>v</sub>aryl, where aryl is selected from: phenyl, pyridyl,  
1H-tetrazol-5-yl, or oxadiazolyl, and where the aryl is optionally  
5 substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, amino, hydroxyl, or -C(O)O(R<sub>2</sub>);

A is:



where x and y are independently 0, 1, 2 or 3;

15 W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>,  
-C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>), 1H-tetrazol-5-yl,  
3-amino-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl,  
5-amino-1,2,4-oxadiazol-3-yl, and 5-methyl-1,2,4-oxadiazol-3-yl;

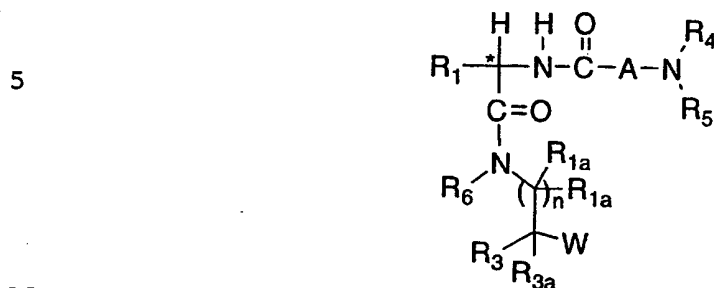
20 m is 0, 1, or 2;  
n is 0 or 1;  
r is 0, 1, 2, or 3;  
v is 0, 1, or 2 ;

25 and pharmaceutically acceptable salts and individual diastereomers  
thereof.

30

- 10 -

More preferred compounds of the instant invention include those of Formula Ib:



Formula Ib

wherein:

R<sub>1</sub> is selected from the group consisting of: C<sub>1</sub>-C<sub>10</sub> alkyl, aryl (C<sub>1</sub>-C<sub>3</sub> alkyl)-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-, and  
 15 aryl (C<sub>0</sub>-C<sub>1</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, where K is O or S(O)<sub>m</sub> and aryl is selected from: phenyl, pyridyl, naphthyl, indolyl, azaindolyl, and benzofuranyl and where the aryl may be further substituted by 1 to 2 of C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>2</sub>, -S(O)<sub>m</sub> R<sub>2</sub>, or -C(O)OR<sub>2</sub>;

20

R<sub>1a</sub> is independently hydrogen or C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one  
 25 atom they may be optionally joined to form a C<sub>5</sub>-C<sub>7</sub> cyclic ring optionally including oxygen, sulfur or NR<sub>2a</sub>;

R<sub>2a</sub> is hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>3</sub> is independently selected from the group consisting of:  
 30 hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl, where heteroaryl is selected from: pyridyl, thiazolyl, indolyl, quinoliny, benzofuranyl, and azaindolyl, and where the phenyl and heteroaryl may be substituted by: C<sub>1</sub>-C<sub>3</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>2</sub>,

- 11 -

$-(CH_2)_rC(O)OR_2$ ,  $-(CH_2)_rC(O)N(R_2)(R_2)$ ,  
 $-(CH_2)_rN(R_6)C(O)N(R_2)(R_2)$ , or  $-(CH_2)_r(R_9)$ ;

R<sub>3a</sub> is hydrogen or C<sub>1</sub> alkyl;

5

R<sub>4</sub> and R<sub>5</sub> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or substituted C<sub>1</sub>-C<sub>3</sub> alkyl where the substituents are selected from: 1 to 5 of halogen, 1 to 3 of hydroxyl, S(O)<sub>m</sub> (C<sub>1</sub>-C<sub>6</sub> alkyl), and phenyl;

10 R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

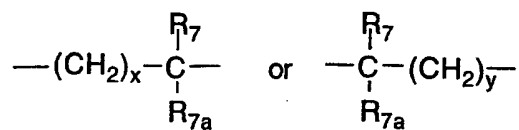
R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>2</sub> alkyl, phenyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from: imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR<sub>2</sub>, and -S(O)<sub>m</sub>R<sub>2</sub>, or R<sub>7</sub> and R<sub>7a</sub>  
15 can independently be joined to one of R<sub>4</sub> and R<sub>5</sub> groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R<sub>7</sub> or R<sub>7a</sub> groups to form a 5 or 6 membered ring; or R<sub>7</sub> and R<sub>7a</sub> can be joined to one another to form a C<sub>3</sub> cycloalkyl;

20 R<sub>8</sub> is selected from the group consisting of:  
hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl groups may be substituted by a substituent selected from the group consisting of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting of:  
25 phenyl, indolyl, 7-azaindolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen, or 1 to 2 of C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>9</sub> is (CH<sub>2</sub>)<sub>v</sub>aryl, where aryl is selected from: 1H-tetrazol-5-yl, and  
30 oxadiazolyl, and where the aryl is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, amino, or hydroxyl;

- 12 -

A is:



5

where x and y are independently 0 or 1;

W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>,  
 -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>), 1H-tetrazol-5-yl,  
 10 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

m is 0, 1, or 2;

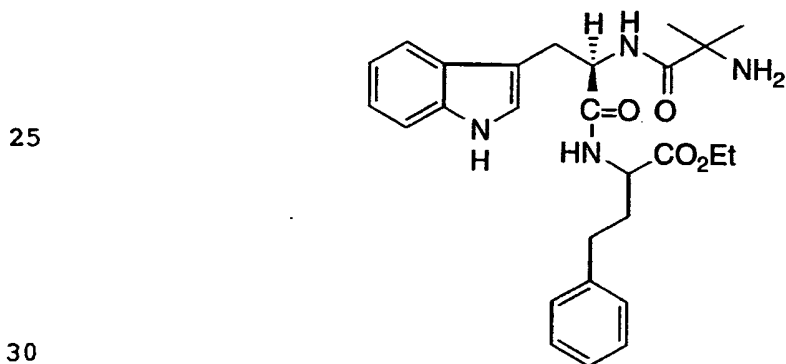
n is 0 or 1;

r is 0, 1, 2, or 3;

15 v is 0, 1, or 2 ;

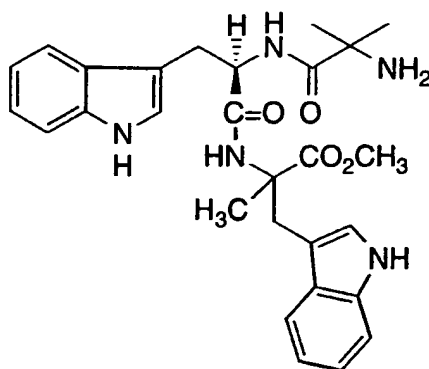
and pharmaceutically acceptable salts and individual diastereomers thereof.

20 The most preferred growth hormone releasing compounds of the present invention include the following:



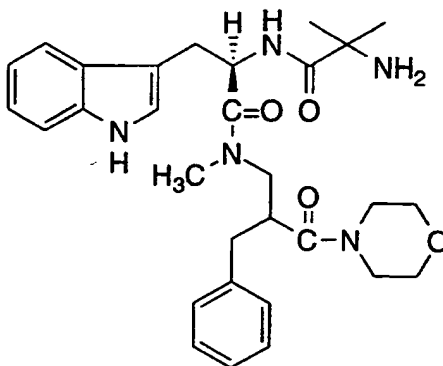
- 13 -

5



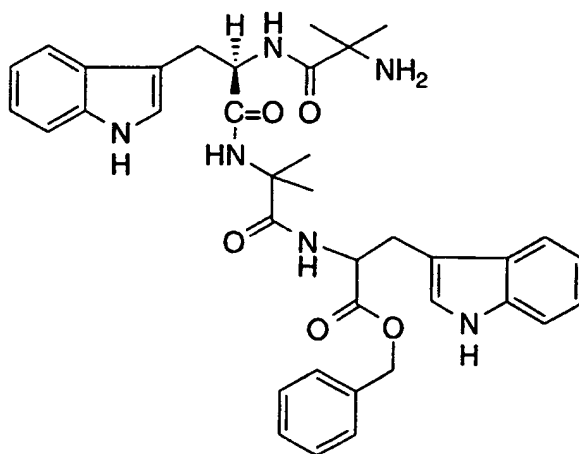
10

15



20

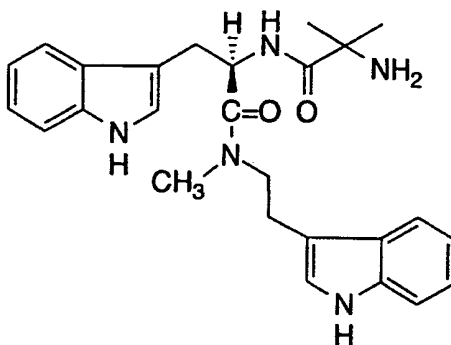
25



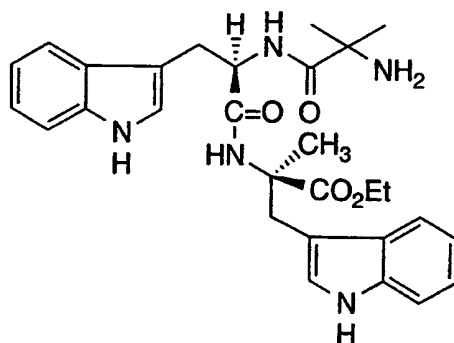
30

- 14 -

5

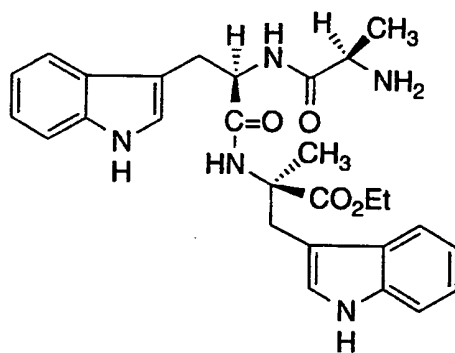


10



15

20

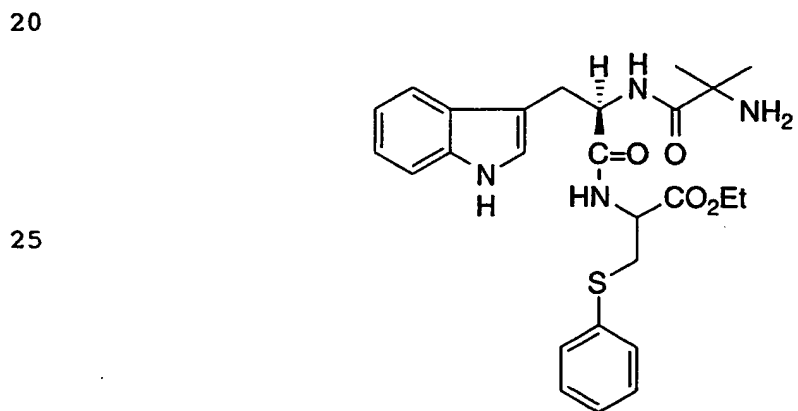
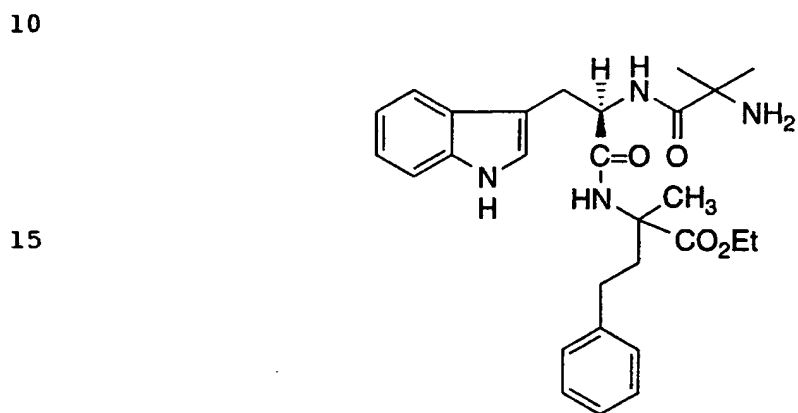
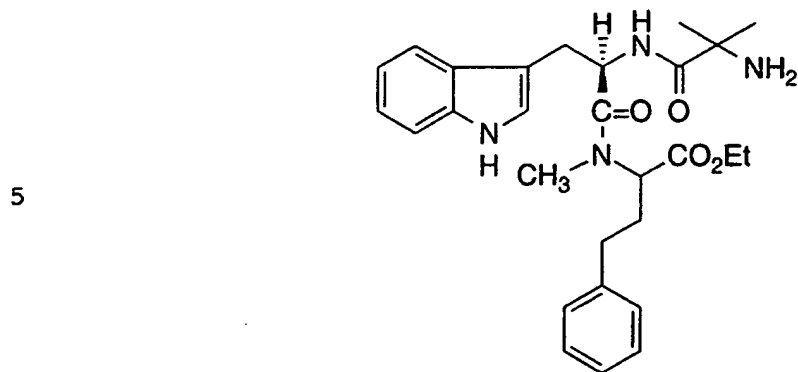


25

30



- 15 -



30 and their pharmaceutically acceptable salts and individual diastereomers thereof, where not otherwise specified.

Throughout the instant application, the following abbreviations are used with the following meanings:

- 16 -

	BOC	t-butyloxycarbonyl
	BOP	Benzotriazol-1-yloxy tris(dimethylamino)- phosphonium hexafluorophosphate
	CBZ	Benzyloxycarbonyl
5	DIBAL-H	diisobutylaluminum hydride
	DMF	N,N-dimethylformamide
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi- imide hydrochloride
	FAB-MS	Fast atom bombardment-mass spectroscopy
10	GHRP	Growth hormone releasing peptide
	HOBT	Hydroxybenztriazole
	LAH	Lithium aluminum hydride
	HPLC	High pressure liquid chromatography
	MHz	Megahertz
15	MPLC	Medium pressure liquid chromatography
	NMM	N-Methylmorpholine
	NMR	Nuclear Magnetic Resonance
	PLC	Preparative liquid chromatography
	RPLC	Reverse phase liquid chromatography
20	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TMS	Tetramethylsilane

25 The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above.

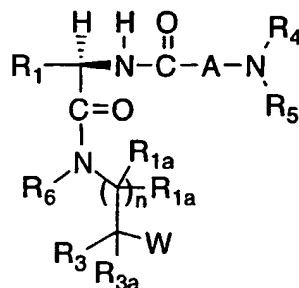
30 Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the instant invention. Compounds which are more active as growth hormone secretagogues and, therefore are preferred, are those in

- 17 -

which the nitrogen substituent is above and the hydrogen atom is below the plane of the structure as represented in Formula II. An equivalent representation places R<sup>1</sup> and the N-substituent in the plane of the structure with the C=O group above the plane of the structure.

5

10



Formula Ia

where R<sub>1</sub>, R<sub>3</sub>, R<sub>3a</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, A, W and n are as defined above.

15

The configuration at the carbon atom bearing R<sub>1</sub> corresponds to that present in a D-amino acid. In most cases, this is also designated as an R-configuration although this will vary according to the value of R<sub>1</sub> used in making the R- or S- stereochemical assignments.

20

Both absolute configurations at the carbon atom bearing W are consistent with activity when n is 2 and this is also true when n is 0, although the configuration corresponding to as (D)- amino acid is then preferred. The absolute stereochemistry of the compounds of this invention may be determined by the X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, containing

25

an asymmetric center of known configuration.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

30

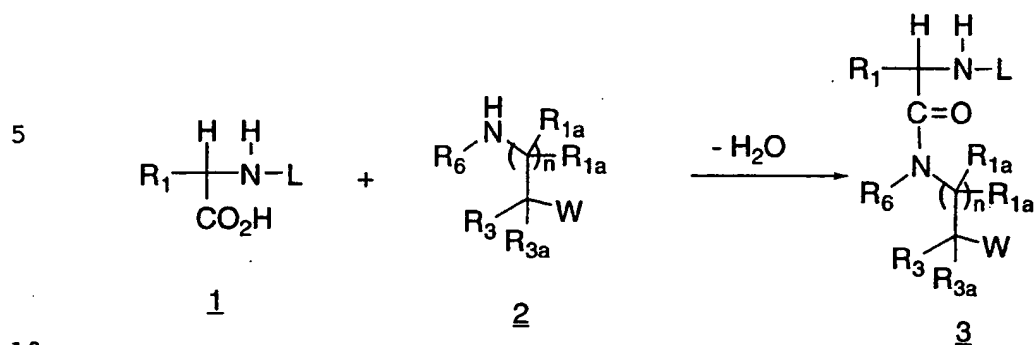
- 18 -

The preparation of compounds of Formula I of the present invention can be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

5           The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to  
10 facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present are found in Greene, T; Wuts, P. G. M. Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, NY (1991). CBZ and BOC were used extensively in the syntheses of this invention,  
15 and their removal conditions are known to those skilled in the art. Removal of CBZ groups can be achieved by a number of methods, for example, catalytic hydrogenation with hydrogen in the presence of palladium catalyst in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other  
20 potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol, with a strong acid, such as trifluoroacetic acid  
25 (TFA) or hydrochloric acid (HCl).

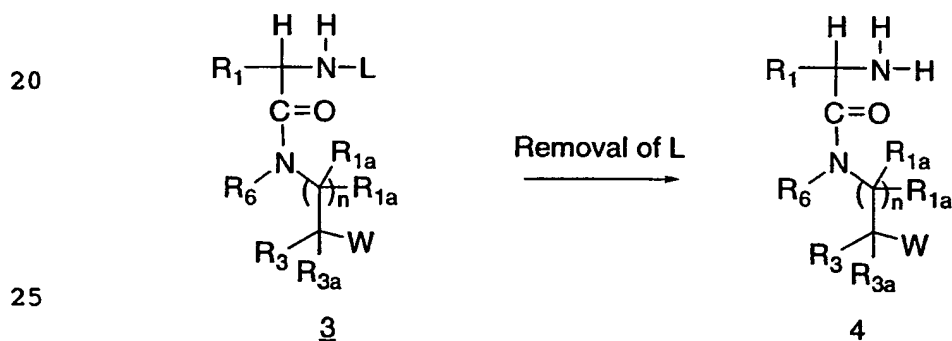
The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. Synthesis of Optically  
30 Active  $\alpha$ -Amino Acids, Pergamon Press: Oxford, 1989). The skills required in carrying out the reaction and purification of the resulting reaction products are known to those skilled in the art. Purification procedures include crystallization, normal phase or reverse phase chromatography.

- 19 -

SCHEME 1

Intermediates of formula 3 can be synthesized as described in Scheme 1. Coupling of amine of formula 2, whose preparations are described later if they are not commercially available, to protected amino acids of formula 1, wherein L is a suitable protecting group, is

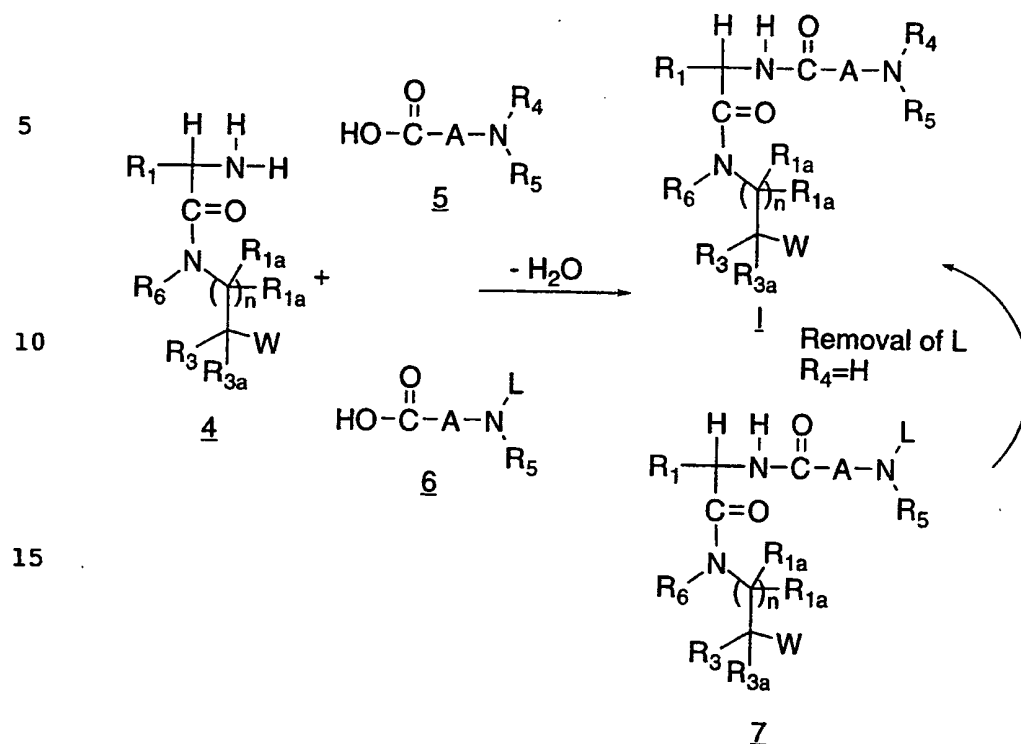
15 conveniently carried out under standard peptide coupling conditions.

SCHEME 2

Conversion of 3 to intermediates 4 can be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)

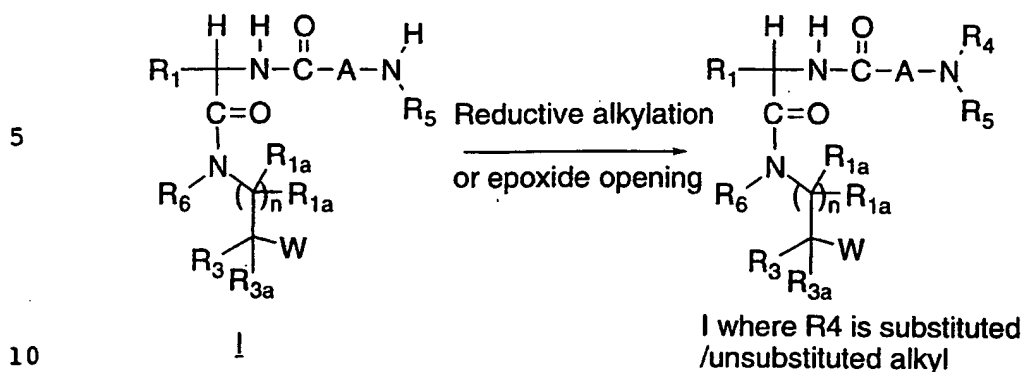
30

- 20 -

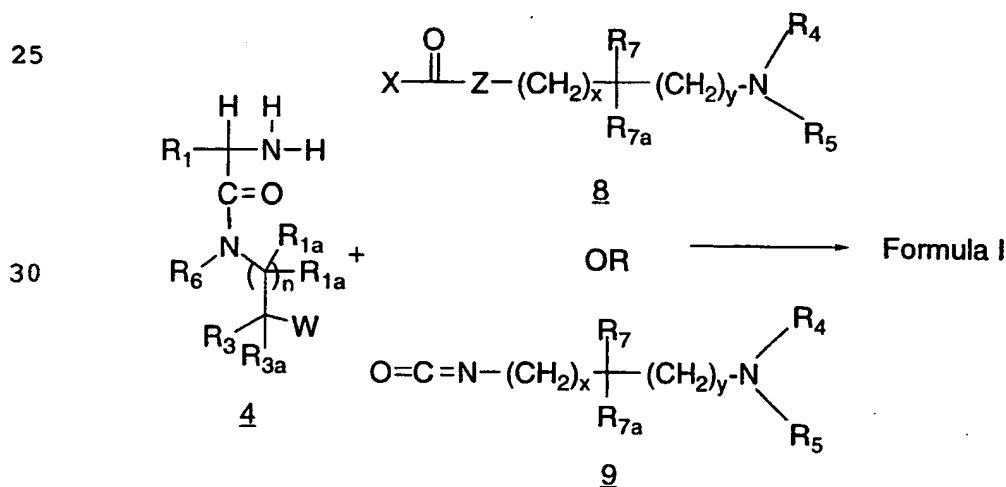
SCHEME 3

Intermediates of formula 5, wherein A is connected to the carbonyl by a carbon atom and thus A is  $-(CH_2)_x-C(R_7)(R_{7a})-(CH_2)_y-$  can be coupled as shown in Scheme 3 to intermediates of formula 4 under the standard peptide coupling reaction conditions. The amino acids 5, as amino acids 1, are either commercially available or can be synthesized. Also if R<sub>4</sub> or R<sub>5</sub> is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein L is a protecting group as defined above. Removal of L in 7 affords I, where R<sub>4</sub> = H, can be carried out under conditions known in the art.

- 21 -

SCHEME 4

Compounds of formula I wherein R4 and/or R5 is a hydrogen can be further elaborated to new compounds I (with preferred side chains R4 = CH<sub>2</sub>-CH(OH)-CH<sub>2</sub>X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in an protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

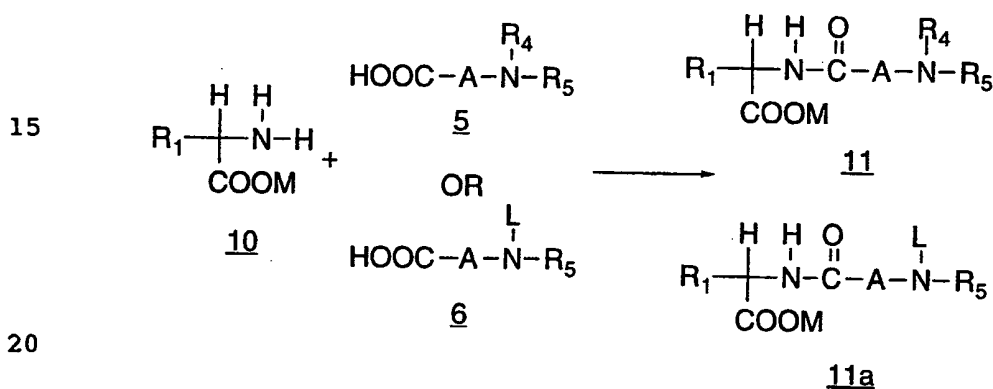
SCHEME 5

- 22 -

Compounds of formula I, wherein A is Z-(CH<sub>2</sub>)<sub>x</sub>-C(R<sub>7</sub>)(R<sub>7a</sub>)-(CH<sub>2</sub>)<sub>y</sub> and Z is N-R<sub>2</sub> or O can be prepared as shown in Scheme 5 by reacting 4 with reagents 8, wherein X is a good leaving group such as Cl, Br, I, or imidazole. Alternatively, 4 can be reacted with an isocyanate of formula 9 in an inert solvent such as 1,2-dichloroethane results in compound of formula I where Z is NH.

The compounds of general formula I of the present invention can also be prepared in a convergent manner as described in reaction Schemes 6, 7 and 8.

### SCHEME 6



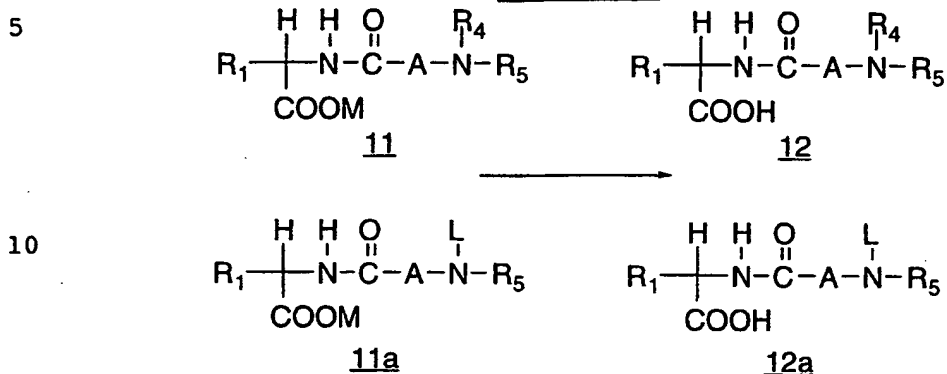
The carboxylic acid protected amino acid derivatives 10 are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of the amino acid with an alcohol in the presence of an acid such as hydrochloric acid or p-toluenesulfonic acid and azeotropic removal of water. Other reactions includes the reaction of a protected amino acid with a diazoalkane, or with an alcohol and an acid activating agent such as EDC, DCC in the presence of a catalyst such as DMAP and removal of the protecting group L.

Intermediates of formula 11 or 11a, can be prepared as shown in Scheme 6 by coupling of amino acid ester 10 to amino acids of



- 23 -

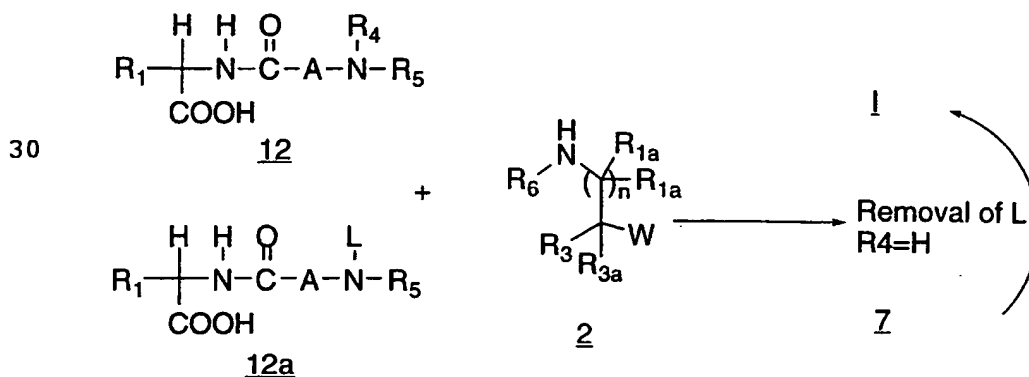
formula 5 or 6. When a urea or urethan linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 5.

SCHEME 7

15 Conversion of the ester 11 or 11a to intermediate acids 12 or 12a can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by

20 a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.* 1982, 42, 587).

25

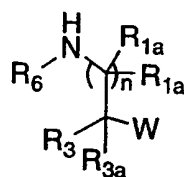
SCHEME 8

- 24 -

Acid 12 or 12a can then be elaborated to I or compound 7 as described in Scheme 8. Coupling amines of formula 2 to acids of formula 12 or 12a, wherein L is a suitable protecting group, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of 7 to I is achieved by removal of the protecting group L. When R<sub>4</sub> and/or R<sub>5</sub> is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

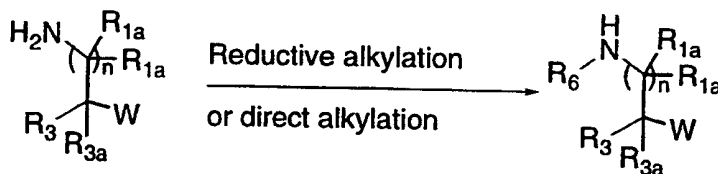
Alternatively, the compounds of this invention can be synthesized by solid phase peptide synthesis.

Compounds of formula 2:



where W is carboxylic acid or derivative, are amino acids or derivatives, most of which are commercially available or known in the literature or they are simple conversion products thereof and can be prepared analogously to the known compounds. Some of the methods of synthesizing  $\alpha$ -amino acids are noted above. The methods for the synthesis of  $\beta$ -amino acids are also well documented and these methods include the hydrolysis of substituted  $\beta$ -lactams to afford  $\beta$ -amino acids.

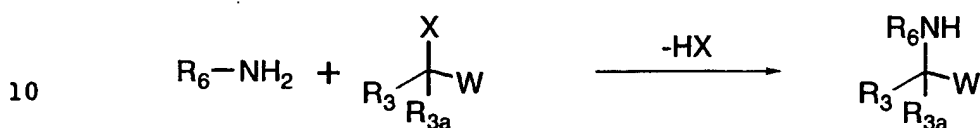
#### SCHEME 9



In cases where R<sub>6</sub> is not hydrogen, it can be introduced by direct alkylation with an alkylating reagent such as alkyl halide or by reductive alkylation with an aldehyde in a protic solvent such as methanol in the presence of a reducing agent such as sodium cyanoborohydride or under hydrogenation conditions in the presence of a

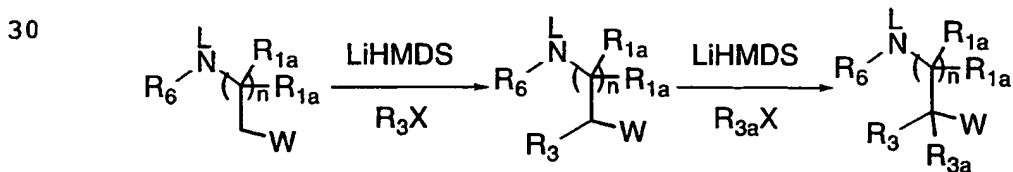
noble metal catalyst such as palladium or its oxide. Alternatively R6 can also be introduced by direct alkylation with alkyl halide of a N-protected amino acid by groups such t-BOC using a strong base such as sodium hydride in an inert solvent such as THF. The t-Boc protecting group can be conveniently removed after the alkylation.

### SCHEME 10



Alternatively, compounds of formula 2 where  $n=0$  can be prepared by reacting the amine  $R_6NH_2$  with an  $\alpha$ -halo carboxylic acid derivative in a inert solvent such as dichloromethane in the presence of a base such as diisopropylethyl amine. The amino acids or their derivatives generated by this synthetic protocols may be racemic. However, procedures for resolving RS- $\alpha$ -amino acid by various methods are known in the literature ( Toone, E. J. and Jones, J. B. *Can. J. Chem.* 1987, 65, 2722; Okamoto, S.; Hijikato, A. *Biochem. Biophys. Res. Commun.* 1981, 101, 440; Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961, Vol. 1, 715-760). Therefore, the separated R- and S- isomers can be prepared by this methodology. Alternatively, the racemic derivatives can be converted directly to growth hormone secretagogues or their intermediates, and the resulting diastereomeric mixtures can be separated at the appropriate stage by chromatography to yield the enantiomerically pure compounds.

**SCHEME 11**



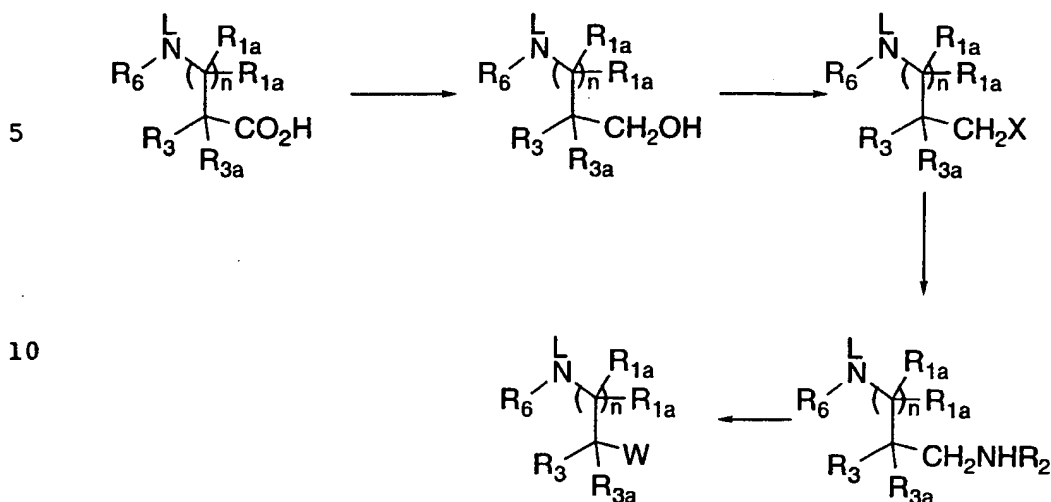
- 26 -

R3 and R3a can be sequentially introduced by alkylation of the corresponding N-protected amino acid derivative where W is electron withdrawing group such as ester, amide, sulphone etc. and as shown in Scheme 11. The reaction can be carried out using LiHMDS as base in an inert solvent such as THF and HMPA and alkyl bromide.

When W = CO<sub>2</sub>H and it is desired to convert this group to ester, amide, acyl sulfonamide, and moieties as defined by W, these transformations can be made according to the conventional methods well documented in the literature and known to those skilled in the art (*The Practice of Peptide Synthesis*, by M. Bodanszky and A. Bodanszky, Springer-Verlag, 1984). For example, esters can be prepared by reacting the amino acid with an alcohol in the presence of an acid catalyst such as p-toluenesulfonic acid under azeotropic conditions. Alternatively, a removable protecting group L such as BOC or CBZ is put onto the NH to which R<sub>6</sub> is attached and the desired transformations are made of the carboxyl group. For example, a carboxyl group can be activated with reagents such as EDC, DCC and BOP in an inert solvent such as dichloromethane in the presence of a catalyst such as DMAP or HOBT and then reacted with alcohols or amines to provide esters and amides respectively.

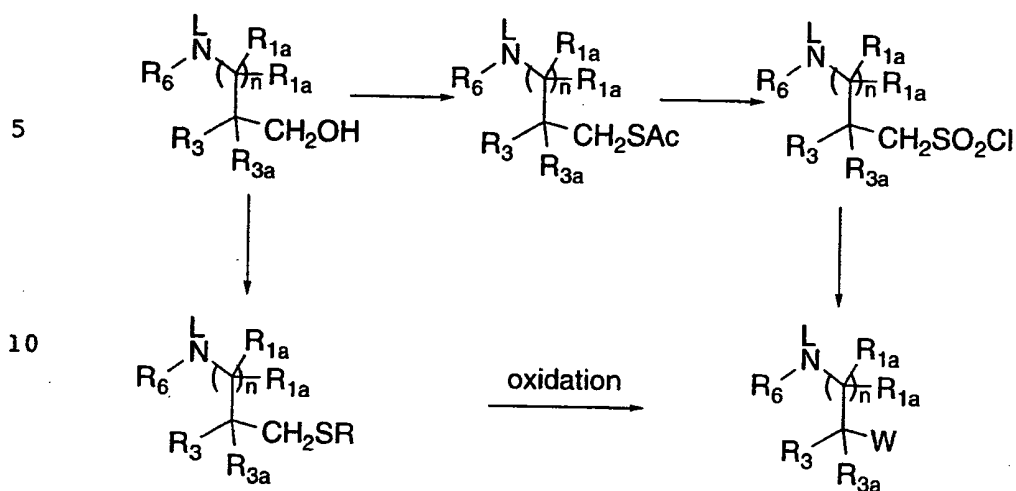
The carboxylic acid can also be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in *J. Org. Chem.* 1992, 57, 7194-7208. The resulting acid and/or ester can be converted to the next higher homologue, and so on and so forth.

- 27 -

SCHEME 12

Reduction of a carboxyl group with a reducing agent such as borane or DIBALH as shown in Scheme 12 affords the corresponding alcohol which can be alkylated or esterified or converted to a reactive leaving group X using, for example, mesyl chloride. Displacement of the X group with amines or equivalents affords amino products or intermediates which may, in turn, be further reacted with sulfonyl chlorides, acyl chlorides or isocyanates to produce sulfonamides, amides or ureas as defined by W.

- 28 -

SCHEME 13

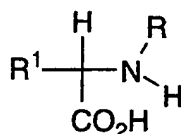
As illustrated in Scheme 13, displacement of the X group with thiols or thiocarboxylic acid affords thioether or thio ester products. Alternatively, the thioethers and thioesters can be prepared directly from the alcohol under the Mitsunobu reaction conditions (Volante, R.P. Tetrahedron Lett. 1981, 22, 3119-3122). Thioethers can be oxidized, for example, to sulfoxides with sodium periodate and to sulfones with OXONE®. Thioesters can be converted to thiols which can be oxidized by chlorine to afford sulfonyl chloride which can be converted to sulfonamide by reacting with amine.

Other functional group transformations which are required to generate the groups specified by W including homologation reactions and the formation of tetrazoles and oxadiazoles are well known in the art and, for example, are to be found in the annual volumes of Theilheimer's Synthetic Methods of Organic Chemistry. When W is hydrogen in formula 2, most of the amines of formula 2 are known in the literature or they can be prepared by standard methods, for example, by the reduction of nitriles or carboxamides, the reductive amination of aldehydes or ketones or by the reaction of alkyl or arylalkyl halides with ammonia or with a primary or secondary amine.

The compounds of the present invention may be prepared from a variety of substituted natural and unnatural amino acids of

- 29 -

formulas 31. The preparation of many of these acids is described in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "Synthesis of Optically Active  $\alpha$ -Amino Acids" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



31

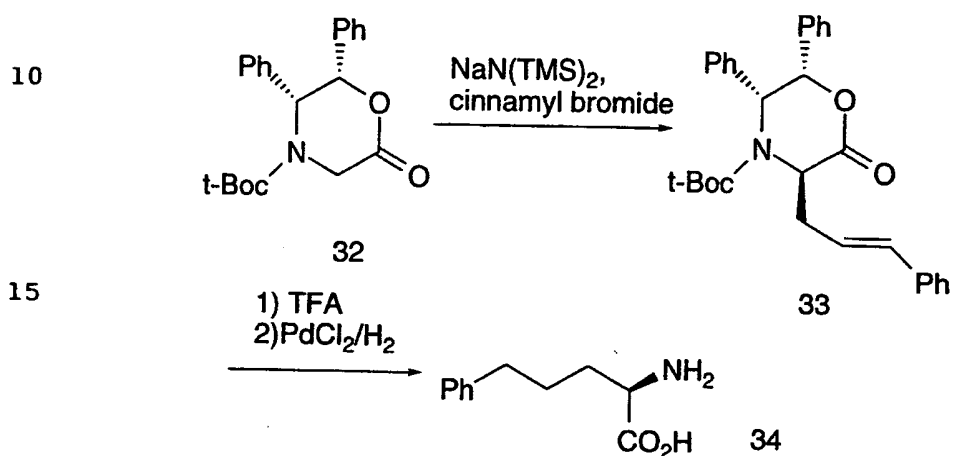
amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in J. Am. Chem. Soc., 111, 6354-6364 (1989).

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (J. Am. Chem. Soc., 108, 6394-6395, 6395-6397, and 6397-6399 (1986)), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (J. Am. Chem. Soc., 114, 1906 (1992); Tetrahedron Lett., 28, 32 (1987)), (3) diastereoselective alkylation of chiral glycine enolate synthons (J. Am. Chem. Soc., 113, 9276 (1991); J. Org. Chem., 54, 3916 (1989)), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate

- 30 -

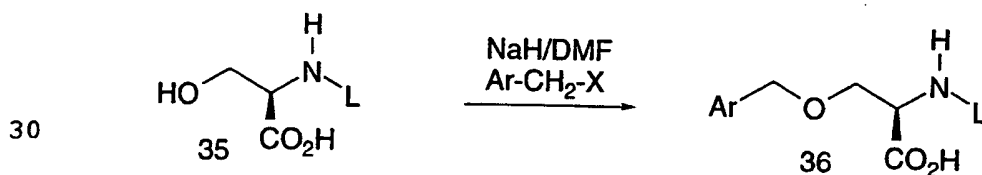
synthon (*J. Am. Chem. Soc.*, **108**, 1103 (1986)), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives (*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL; Vol 5 (1985)), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.*, **17**, 176 (1978)).

## SCHEME 14



20 For example, alkylation of the enolate of diphenyloxazinone 32 (*J. Am. Chem. Soc.*, **113**, 9276 (1991)) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 33 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 34 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a  $\text{PdCl}_2$  catalyst (Scheme 14).

## SCHEME 15



Intermediates of formula 31 which are O-benzyl-(D)-serine derivatives 36 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 35. The protecting group L is

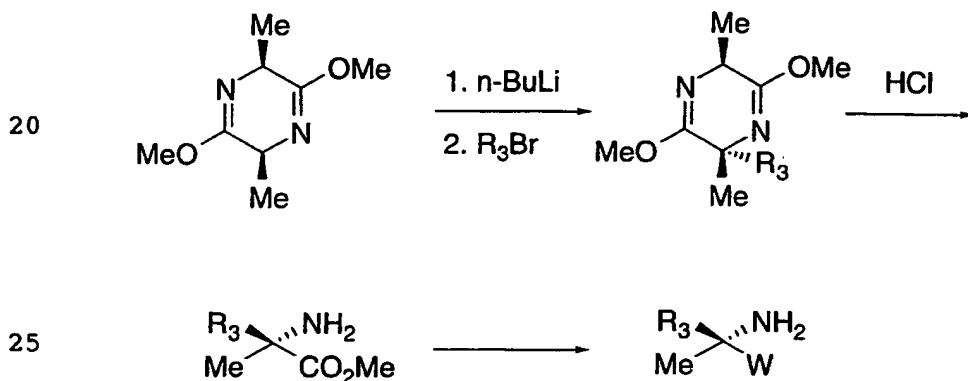


- 31 -

conveniently a BOC or a CBZ group. Benzylation of 35 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of  
 5 benzyl halides (Synthesis, 36 (1989)) as shown in Scheme 15.

The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula 36 include the acid catalyzed benzylation of carboxyl protected intermediates derived from 35 with  
 10 reagents of formula  $\text{ArCH}_2\text{OC}(=\text{NH})\text{CCl}_3$  (O. Yonemitsu *et al.*, Chem. Pharm. Bull., 36, 4244 (1988)). Alternatively, alkylation of the chiral glycine enolates (J. Am. Chem. Soc., 113, 9276 (1991); J. Org. Chem., 54, 3916 (1989)) with  $\text{ArCH}_2\text{OCH}_2\text{X}$  where X is a leaving group affords 36. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved  
 15 by methods described above.

#### SCHEME 16



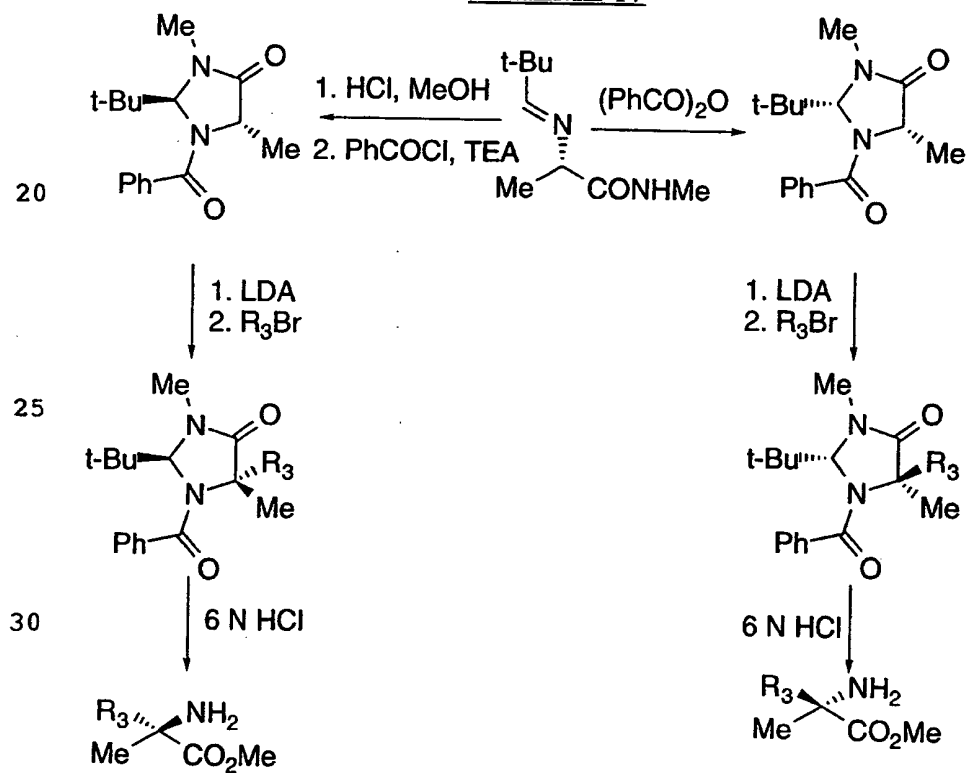
The asymmetric synthesis of  $\alpha,\alpha$ -disubstituted amino acids can be achieved by the bislactim chemistry developed by Schollkopf and coworkers (Schollkopf, U., Tetrahedron, 39, 2085  
 30 (1983)) as illustrated in Scheme 16. Thus, the readily available optically active bislactim can be alkylated with an alkyl or arylalkyl halide to obtain the intermediate shown with high asymmetric induction due to the presence the other methyl group which directs the  $\text{R}_3$  group trans to it. Hydrolysis of this alkylated product yields the

- 32 -

$\alpha$ -methyl amino acid methyl ester. The resulting methyl ester can be converted to groups as defined by W through conventional chemistry as discussed before. Shown in the scheme was the preparation of one enantiomer of the  $\alpha$ -methyl amino acid, the other enantiomer can be prepared in a similar way from starting material of the opposite stereochemistry.

Alternatively, the asymmetric synthesis of  $\alpha,\alpha$ -disubstituted amino acids can be achieved by the alkylation of the Schiff base of L-alanine methyl ester and chiral auxiliary 1,2,3,4-di-O-cyclohexylidene- $\alpha$ -D-galacto-hexo-1,5-dialdopyranose which was also developed by Schollkopf and coworkers (*Synthesis*, 789 (1983)). The chiral auxiliary is removed by acid hydrolysis to yield the desired  $\alpha$ -methyl amino acids.

SCHEME 17

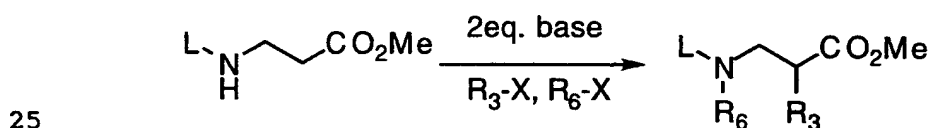


- 33 -

Another asymmetric synthesis of  $\alpha$ -methyl amino acids can be achieved by the methods developed by Seebach and coworkers which involves reproduction of chirality without using a chiral auxiliary (Naef, R, and Seebach, D., Helv. Chim. Acta., **68**, 135 (1985)) as shown in Scheme 17. The Schiff base of trimethylacetaldehyde and L-AlaNHMe can be converted to the two imidazolindinones as shown in the scheme under different reaction conditions. Alkylation and acid hydrolysis yields the amino acids. Thus both enantiomers of the amino acid can be prepared from the same intermediate.

The compounds of general formula 2 ( $n=1$ ) of the present invention are either commercially available or known compounds which can be prepared by literature procedures. Illustrated here are some, but by no means all the methods available for their preparation. For example, the synthesis of  $\alpha$ -substituted  $\beta$ -amino acids and  $\alpha,\beta$ -disubstituted  $\beta$ -amino acids can be prepared from the nucleophilic addition of an excess of hydroxyamine to the corresponding  $\alpha$ - or  $\beta$ -substituted  $\alpha,\beta$ -unsaturated acids (Organic Syntheses, Collect. Vol. III; Wiley: New York, 91 (1955)).

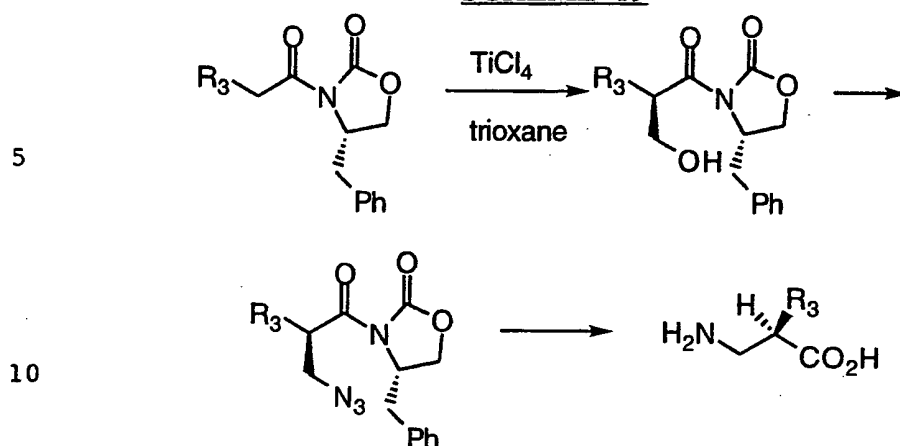
#### SCHEME 18



In addition, the synthesis of  $\alpha$ -substituted- $\beta$ -amino acids can be prepared from alkylation of a dianion of  $\beta$ -alanine as detailed in Scheme 18 involving stepwise alkylation first of the more reactive carbon anion. In these two procedures, the  $\beta$ -amino acids are obtained in racemic form. Several methods exist to resolve (D,L) amino acids. One of the most common methods is to resolve an amino or carboxyl protected intermediate by crystallization of salts derived from optically active acids or amines.

- 34 -

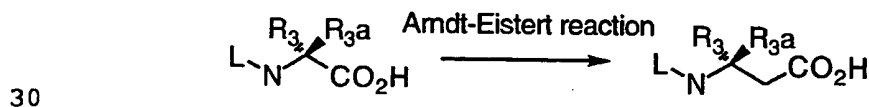
## SCHEME 19



Alternatively, the asymmetric synthesis of enantiomerically pure  $\beta$ -amino acids is available. For example, E. Juaristi and J. Escalante (*J. Org. Chem.*, 58, 2282 (1993)) have used 1-benzoyl-3,6-(S)-dimethylperhydropyrimidin-4-one as an intermediate to synthesize in enantiomerically pure form  $\alpha,\beta$ -disubstituted- $\beta$ -amino acids. Specifically, the synthesis of a signal enantiomer of  $\alpha$ -substituted- $\beta$ -amino acids can be achieved by 1,4-asymmetric induction in the alkylation of a titanium enolate (D. A. Evans et al., *J. Am. Chem. Soc.*, 112, 8215 (1990)) as detailed in Scheme 19. Removal of the chiral template from the alkylation product can be carried out by a number of methods familiar to those skilled in the art, including the lithium benzyloxide protocol detailed by D. A. Evans et al., *J. Am. Chem. Soc.*, 104, 1737 (1982)).

25

## SCHEME 20



$\beta$ -Substituted- $\beta$ -amino acids or  $\beta,\beta$ -disubstituted- $\beta$ -amino acids can be obtained from the corresponding  $\alpha$ -amino acids or  $\alpha$ -substituted amino acids with full retention of configuration using the Arndt-Eistert method (*Tetrahedron*, 43, 3509, (1987)) depicted in

- 35 -

Scheme 20. The  $\alpha$ -amino acids and  $\alpha$ -substituted amino acids can be prepared by methods familiar to those skilled in the art, including the procedures described in Schemes 16 and 17. The protecting group L can be removed through conventional chemistry. The natural and  
5 unnatural amino acids of general formula 2 can be elaborated to compounds of formula I by using chemistry described above.

It is noted that in some situations the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

10 The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, et al., Science, 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, the intrinsic growth hormone secretagogue activities of the compounds  
15 of the present invention may be demonstrated in this assay.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence  
20 growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that  
25 somatostatin inhibits growth hormone release and that the growth hormone releasing factor (GRF) stimulates its release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g.,  
30 cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed

- 36 -

to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to  
5 elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially  
10 important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable  
15 of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of  
20 the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active  
25 ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side  
30 effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens,  $\beta$ -agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins,

- 37 -

compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

5 A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO  
10 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or  $\alpha$ -adrenergic agonists such as clonidine or serotonin 5HT<sub>1D</sub> agonists such as sumatriptan or agents which inhibit somatostatin or its release such as physostigmine  
15 and pyridostigmine.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same  
20 effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth  
25 retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and  
30 Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia, treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrody-

- 38 -

splasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; to stimulate thymic development and prevent the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.



- 39 -

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with  
5 the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in  
10 dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone  
15 secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases. Trends in Endocrinol. Metab., 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-  
20 175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

25 The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

30 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than

- 40 -

inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

5                   Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include  
10                   adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

                  Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or  
15                   vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as  
                  preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by  
20                   incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be  
                  manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium  
                  immediately before use.

                  Compositions for rectal or vaginal administration are  
25                   preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

                  Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

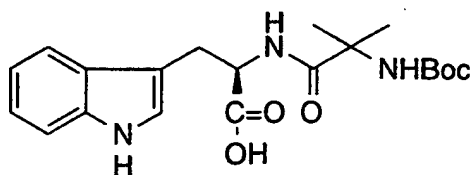
                  The dosage of active ingredient in the compositions of this  
30                   invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are

- 41 -

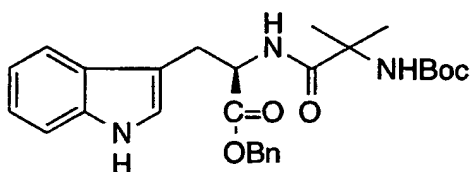
administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

INTERMEDIATE 1



Step A:



To 5.0 g (16.5 mmole) of the commercially available N-t-BOC-D-tryptophan in 100 mL of chloroform was added 1.80 mL (16.5 mmole) of benzyl alcohol, 0.20 g (1.65 mmole) of 4-N,N-dimethylamino pyridine (DMAP), and 3.20 g of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organic solution was washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil.

To a solution of this oil in 10 mL of dichloromethane was added 20 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated, basified carefully with saturated aqueous sodium bicarbonate solution, and extracted with chloroform (2X100 mL). The combined organic solution were washed with brine (100 mL), dried

- 42 -

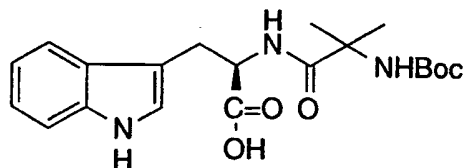
over potassium carbonate, filtered, and concentrated to give 5.46 g of the amine as a brown oil which was used without purification.

To 5.46 g of the above product in 100 mL of chloroform was added 3.40 g (22.2 mmole) of HOBt, 4.60 g (22.2 mmole) of N-BOC- $\alpha$ -methyl alanine, and 5.32 g (28.0 mmole) of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organic solution were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 6.94 g of the product as a thick oil. Flash chromatography (200 g SiO<sub>2</sub>; hexane-ethyl acetate as eluent) gave 4.75 g of the desired material as a colorless foam.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz)  $\delta$  8.48 (bs, 1H), 7.54 (bd, 1H), 7.38-7.23 (m, 3H), 7.19 (bd, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (bs, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

Step B:

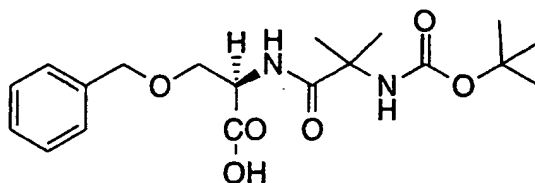
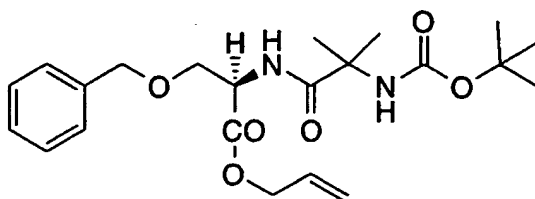
20



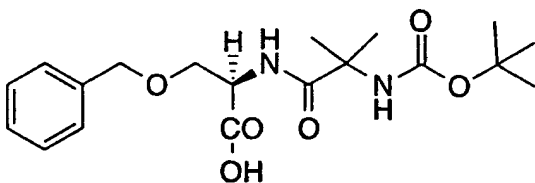
To a solution of 4.75 g of the material from Step A in 100 mL of ethanol was added 1.0 g of 10% Pd/C and stirred at RT under a H<sub>2</sub> balloon for 18h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 2.96 g of the acid as a colorless foam.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz)  $\delta$  8.60 (bs, 1H), 7.55 (d, 1H), 7.26-6.90 (m, 3H), 6.88 (bd, 1H), 4.80 (m, 1H), 3.32 (2dd, 2H), 1.37 (s, 3H), 1.35 (s, 12H)

- 43 -

INTERMEDIATE 2Step A:

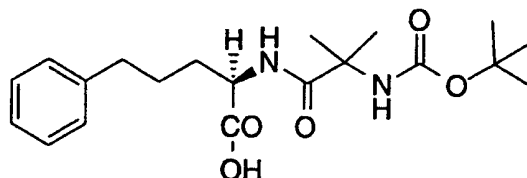
Prepared from N-tBOC-O-benzyl-D-serine and allyl alcohol by the procedure described in Intermediate 1, Step A and subsequent coupling to N-BOC- $\alpha$ -methylalanine to give the desired compound.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B:

To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was separated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.

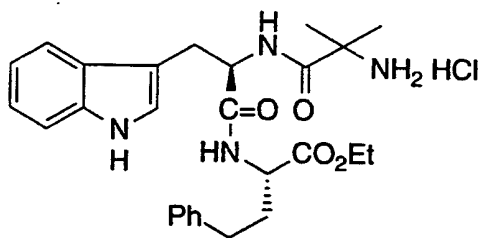
- 44 -

<sup>1</sup>H NMR (400Hz, CD<sub>3</sub>OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

INTERMEDIATE 3

This intermediate was synthesized as described in Step A and B of Intermediate 1, but (2R)-N-t-BOC-5-phenylpentanoic acid (H. K. Chenault et al., *J. Am. Chem. Soc.*, **111**, 6354-6364 (1989)) was used in place of N-t-BOC-(D)-Tryptophan.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

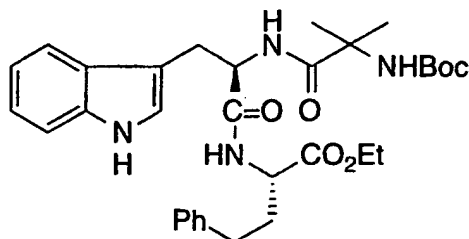
EXAMPLE 1Step A: L-HomoPhe ethyl ester hydrochloride

Thionyl chloride (0.41 mL, 5.58 mmol) was added slowly into stirred ethanol (20 mL) at 0°, the mixture was stirred for 10 min., and to which was added L-HomoPheOH (1g, 5.58 mmol). The mixture was refluxed for 2 hours and then allowed to cool to room temperature. The material was then concentrated and taken to dryness in vacuo to give the title compound (1.35 g).

- 45 -

Step B:

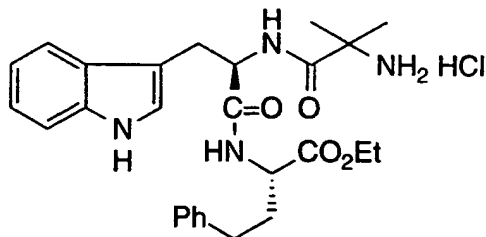
5



To a solution of L-HomoPhe ethyl ester hydrochloride (75 mg, 0.255 mmol), Intermediate 1 (100 mg, 0.255 mmol), HOBT (34 mg), N-methylmorpholine (0.033 mL) in dichloromethane (15 mL) was added EDC (100 mg). The reaction mixture was stirred at room temperature overnight. The solution was diluted with ethyl acetate and washed subsequently with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the desired compound (120.6 mg). FAB-MS calc. for C<sub>32</sub>H<sub>42</sub>N<sub>4</sub>O<sub>6</sub>: 578; found: 579 (M+H).

20 Step C:

25



A solution of the intermediate from previous step (120 mg) in ethyl acetate (5 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate. The residue was then redissolved in dichloromethane and

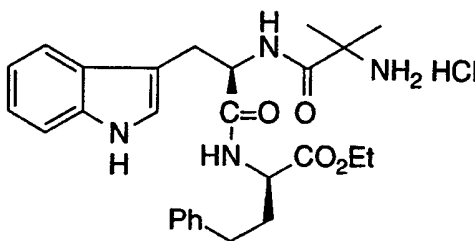
- 46 -

hexane was added followed by evaporation in vacuo to afford the product as a solid (100 mg).

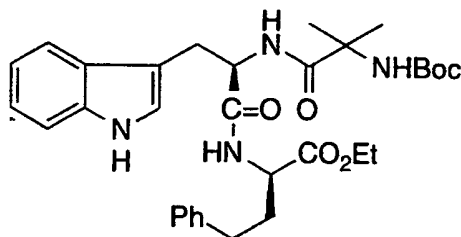
FAB-MS calc. for  $C_{27}H_{34}N_4O_4$ : 478; found: 479 (M+H).

$^1H$ NMR (400 MHz,  $CD_3OD$ ): 8.29, 8.05(2d, 1H), 7.64 (d,  $J=7.5$  Hz, 1H), 7.30-7.00 (m, 9H), 4.85 (m, 1H), 4.23-4.17 (m, 1H), 4.11 (q,  $J=7.1$  Hz, 2H), 3.34-3.10 (dd,  $J_1=7.1$  Hz, 1H), 3.16 (dd,  $J=8.2$  Hz, 14.2 Hz, 1H), 2.34-2.29 (m, 2H), 1.95-1.89 (m, 1H), 1.79-1.74 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.22 (t,  $J=7$  Hz, 3H).

## EXAMPLE 2



### Step A:



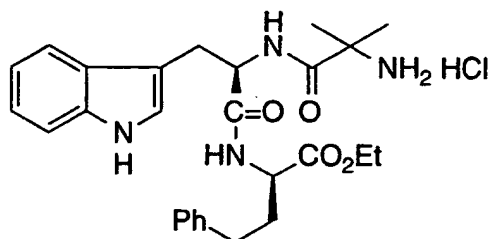
Prepared by the procedure described in Example 1, Step B from D-HomoPhe ethyl ester hydrochloride (75 mg, 0.255 mmol), Intermediate 1 (100 mg, 0.255 mmol), HOBT (34 mg.), N-methyl morpholine (0.033 mL; 0.255 mmol), and EDC (100 mg). Product: 108 mg. FAB-MS calc. for  $C_{32}H_{42}N_4O_6$ : 578; found: 579 (M+H).



- 47 -

Step B:

5



Prepared by the procedure described in Example 1, Step C  
 10 from the intermediate from previous step (106 mg) and HCl gas in ethyl  
 acetate (3 mL) at 0°C. Reaction time: 1 hour. Product: 94.5 mg.  
 FAB-MS calc. for C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>: 478; found: 479 (M+H).  
<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): 8.54, 7.98 (2d, 1H), 7.67 (d, J=7.7 Hz,  
 1H), 7.32 (d, J=8.1 Hz, 1H), 7.27-7.14 (m, 6H), 7.08 (t, J=7.1 Hz, 1H),  
 15 7.01 (t, J=7.1 Hz, 1H), 4.85 (m, 1H), 4.38-4.33 (m, 1H), 4.13 (q, J=7.1  
 Hz, 2H), 3.36 (dd, J=5.4 Hz, 14.5 Hz, 1H), 3.16 (dd, J=9.5 Hz, 14.5 Hz,  
 1H), 2.73-2.59 (m, 2H), 2.13-2.07 (m, 1H), 2.03-1.96 (m, 1H), 1.54 (s,  
 3H), 1.31 (s, 3H), 1.24 (t, J=7.1 Hz, 3H).

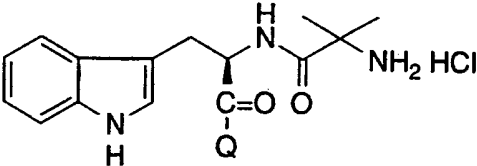
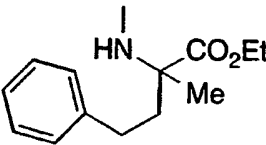
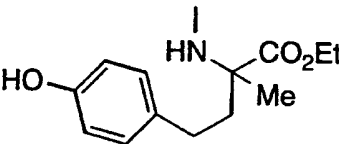
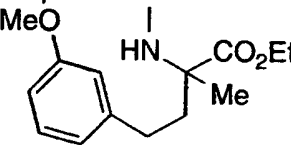
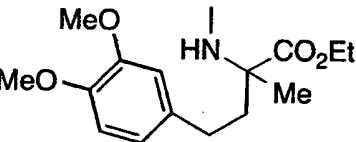
20 The additional products shown in Table I were prepared  
 according to Example 1 Steps A, B and C from the corresponding  
 α-methyl amino acid instead of L-homoPheOH

25

30

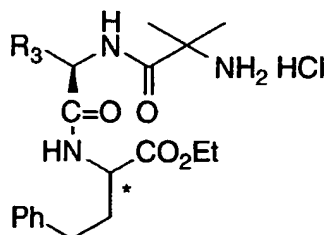
- 48 -

TABLE I: ADDITIONAL EXAMPLES

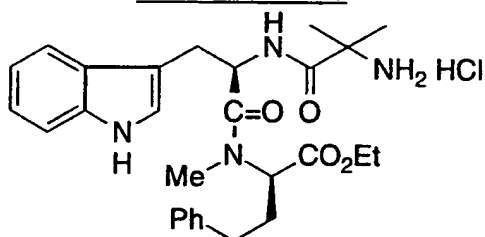
5			
10	entry	Q	MF FAB-MS (M+1)
15	1		C <sub>28</sub> H <sub>36</sub> N <sub>4</sub> O <sub>4</sub> 493
15	2		C <sub>28</sub> H <sub>36</sub> N <sub>4</sub> O <sub>5</sub> 509
20	3		C <sub>29</sub> H <sub>38</sub> N <sub>4</sub> O <sub>5</sub> 523
25	4		C <sub>30</sub> H <sub>40</sub> N <sub>4</sub> O <sub>6</sub> 553

The additional products shown in Table IA were prepared according to Example 1 Steps B and C or Example 2 Steps A and B, using Intermediate 2 and Intermediate 3 and D or L-homophenyl-alanine ethyl ester.

- 49 -

TABLE IA: ADDITIONAL EXAMPLES

entry	R3	*	MF FAB-MS (M+1)
1	PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	D	C <sub>27</sub> H <sub>37</sub> N <sub>3</sub> O <sub>4</sub> 468
2	PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	L	C <sub>27</sub> H <sub>37</sub> N <sub>3</sub> O <sub>4</sub> 468
3	PhCH <sub>2</sub> OCH <sub>2</sub> -	D	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>5</sub> 470
4	PhCH <sub>2</sub> OCH <sub>2</sub> -	L	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>5</sub> 470

EXAMPLE 2AStep A: N-Me-D-homoPheOEt

To a suspension of sodium hydride (60%, 458 mg, washed with hexane) in THF (3 mL) at room temperature under Ar, was added D-Boc-homoPhOH (533 mg, 1.9 mmol) in THF (2mL) via a syringe. After stirring for 5 minutes, iodomethane (1.43 mL) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was slowly added to 1 N sodium bisulfate solution then it was extracted with ethyl acetate twice. The combined organic solution was dried over magnesium sulfate,

- 50 -

evaporated to give a brown solid (700 mg, crude) which was used without further purification.

The solid obtained was dissolved in ethyl acetate (3mL). HCl gas was bubbled through the solution until it was saturated at 0°C. The

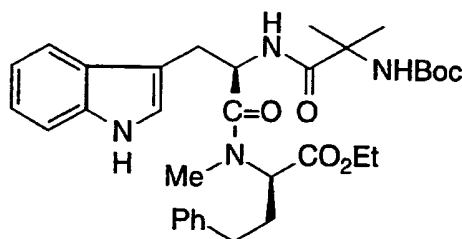
5 reaction mixture was stirred for additional 15 minutes, and it was evaporated to dryness to give N-Me-D-homophenylalanine.

The resulting amino acid was dissolved in 20 mL of acidic ethanol and refluxed for two hours. The solution was evaporated to give the desired product.

10

Step B:

15



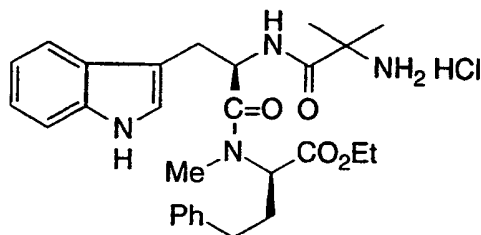
20 Prepared by the procedure described in Example 1, Step B from the intermediate from the previous step (200 mg), Intermediate 1 (200 mg, 0.514 mmol), HOBT (68 mg.), N-methyl morpholine(0.066 mL; 0.514 mmol), and EDC (200 mg). Product: 235.2 mg.

FAB-MS calc. for C<sub>33</sub>H<sub>44</sub>N<sub>4</sub>O<sub>6</sub>: 592; found: 593 (M+H).

25

Step C:

30

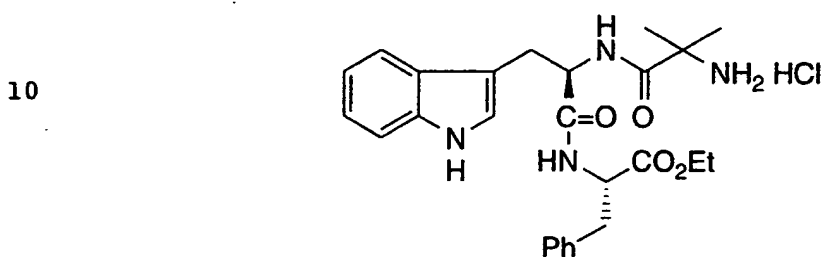


- 51 -

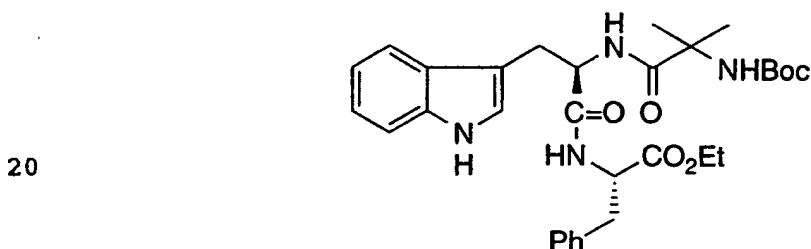
Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (204 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 30 minutes. Product: 186 mg.

5 FAB-MS calc. for C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub>: 492; found: 493 (M+H).

### EXAMPLE 3



15 Step A:

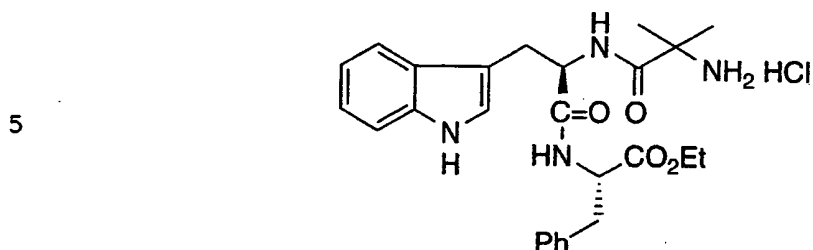


Prepared by the procedure described in Example 1, Step B from L-Phe ethyl ester hydrochloride (176 mg, 0.771 mmol),

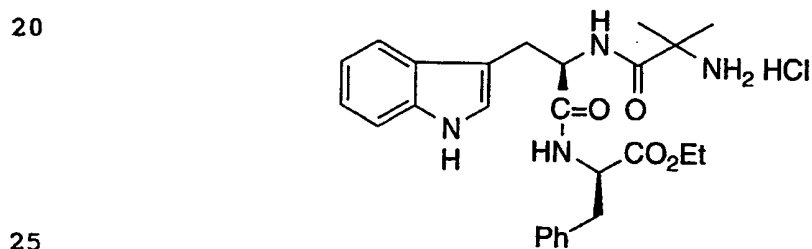
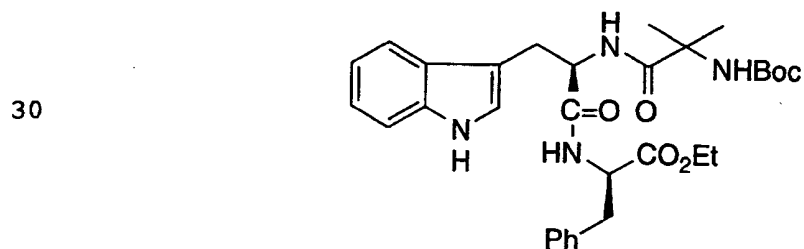
25 Intermediate 1 (200 mg, 0.514 mmol), HOBT (64), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 246 mg. FAB-MS calc. for C<sub>31</sub>H<sub>40</sub>N<sub>4</sub>O<sub>4</sub>: 464; found: 465 (M+H). <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD) : 8.73 (br. s., 1 H), 7.57 (d, J=2.3 Hz, 1H), 7.40-7.00 (m, 9H), 6.97 (s, 1H), 6.71 (br. d, 1H), 4.86 (s, 1H),

30 4.68 (dd, J=6 Hz, 14 Hz, 1H), 4.59 (dd, J=7.3 Hz, 14.3 Hz, 1H), 4.0 (q, 2H), 3.36 (dd, J=5.5 Hz, 14.7 Hz, 1H), 3.20 (dd, J=5.5 Hz, 14.6 Hz, 1H), 2.97 (br. d., J=6.5 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 9H), 1.18 (s, 3H), 1.08 (t, J=7 Hz, 3H).

- 52 -

Step B:

Prepared by the procedure described in Example 1, Step C  
 10 from the intermediate from previous step (240 mg) and HCl gas in ethyl  
 acetate (5 mL) at 0°C. Reaction time: 20 minutes. product: 152.5 mg.  
 FAB-MS calc. for C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>: 464; found: 465 (M+H).  
<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): 8.24-6.94 (m, 11H), 4.79-4.74 (m, 1H),  
 4.64-4.59 (m, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.11 (dd, J=6 Hz, 14.6 Hz,  
 15 1H), 3.01-2.92 (m, 2H), 2.81(dd, J=8.4 Hz, 13.8 Hz, 1H), 1.49 (s, 3H),  
 1.29 (s, 3H), 1.18 (t, J=7 Hz, 3H).

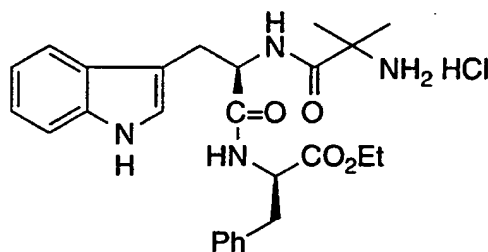
EXAMPLE 4Step A:

- 53 -

Prepared by the procedure described in Example 1, Step B from D-phenylalanine ethyl ester hydrochloride (176 mg, 0.771 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol).  
5 Product: 287 mg. FAB-MS calc. for  $C_{31}H_{40}N_4O_4$ : 464; found: 465 (M+H).

Step B:

10



15

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (280 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 231.7 mg. FAB-MS calc. for  $C_{26}H_{32}N_4O_4$ : 464; found: 465 (M+H).  
20 <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): 8.29-6.94 (m, 11H), 4.79-4.75 (m, 1H), 4.64-4.59 (m, 1 H), 4.10-4.05 (m, 2H), 3.27-2.96 (m, 4H), 1.49 (s, 3H), 1.28 (s, 3H), 1.19-1.15 (m, 3H).

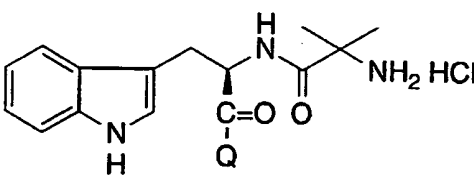
25

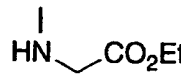
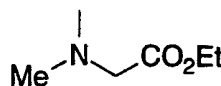
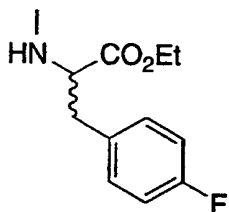
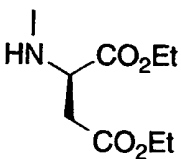
30

- 54 -

The additional examples shown in Table II were prepared according to Example 1 Steps B and C, using Intermediate 1 and commercially available intermediates.

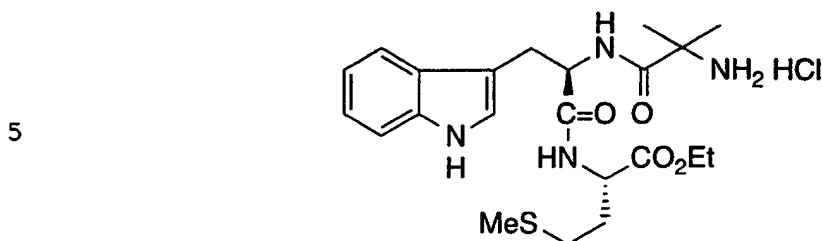
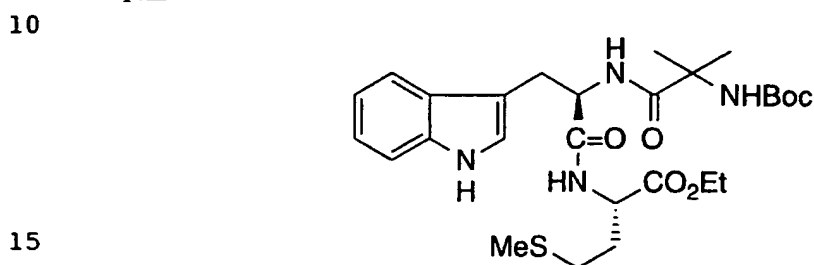
TABLE II: ADDITIONAL EXAMPLES



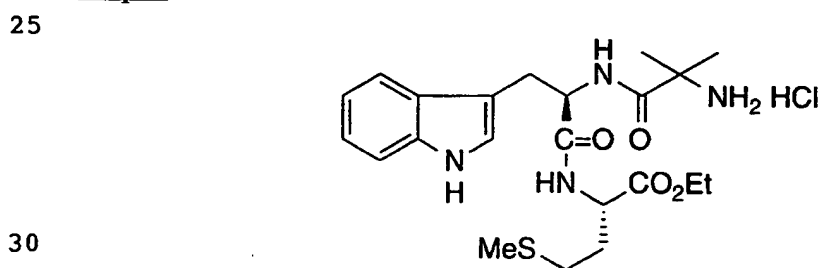
entry	Q	MF FAB-MS (M+1)
1		C <sub>19</sub> H <sub>26</sub> N <sub>4</sub> O <sub>4</sub> 375
2		C <sub>20</sub> H <sub>28</sub> N <sub>4</sub> O <sub>4</sub> 389
3	Ph(CH <sub>2</sub> ) <sub>3</sub> NH-	C <sub>24</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> 407
4		C <sub>26</sub> H <sub>31</sub> N <sub>4</sub> O <sub>4</sub> F 483
5		C <sub>23</sub> H <sub>32</sub> N <sub>4</sub> O <sub>6</sub> 461



- 55 -

EXAMPLE 5Step A:

Prepared by the procedure described in Example 1, Step B from L-methionine ethyl ester hydrochloride (165 mg, 0.771 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 262 mg. FAB-MS calc. for C<sub>27</sub>H<sub>40</sub>N<sub>4</sub>O<sub>6</sub>S: 548; found: 549 (M+H).

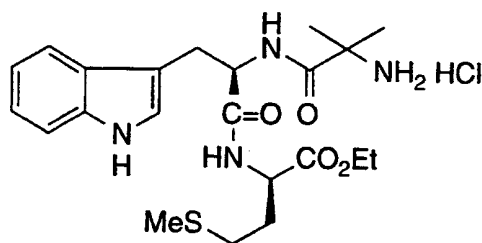
Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (250 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 209.4 mg.

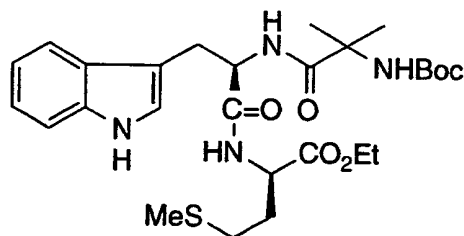
- 56 -

FAB-MS calc. for  $C_{22}H_{32}N_4O_4S$ : 448; found: 449 (M+H).

$^1H$ NMR (400 MHz,  $CD_3OD$ ): 8.26-6.99(m, 6H), 4.82-4.78 (m, 1H),  
 4.42-4.37 (m, 1 H), 4.14 (q, J=7 Hz, 2H), 3.31-3.26(dd, 2H), 3.14 (dd,  
 J=8.0 Hz, 2H), 2.20-2.10 (m, 2H), 1.98 (s, 3H), 1.96-1.87 (m, 1H), 1.81-  
 1.73 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.24 (t, J=7 Hz, 3H).

**EXAMPLE 6**

**Step A:**

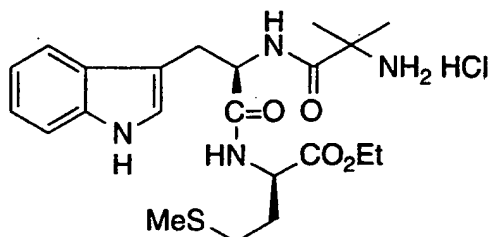


Prepared by the procedure described in Example 1, Step B  
 from D-methionine ethyl ester hydrochloride (165 mg, 0.771 mmol),  
 Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl  
 morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol).  
 Product: 243 mg. FAB-MS calc. for  $C_{27}H_{40}N_4O_6S$ : 548; found: 549  
 (M+H).

- 57 -

Step B:

5

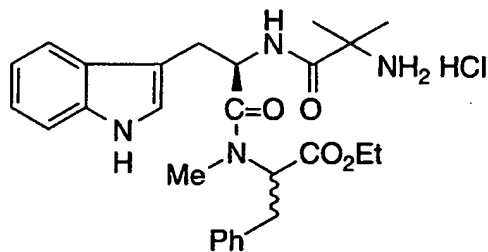


Prepared by the procedure described in Example 1, Step C  
 10 from the intermediate from previous step (240 mg) and HCl gas in ethyl  
 acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 200 mg.  
 FAB-MS calc. for C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S: 448; found: 449 (M+H).  
<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): 8.48, 8.00 (2d, 1H), 7.65 (d, J=7.8 Hz,  
 1H), 7.32 (d, J=8.0 Hz, 1H), 7.15 (s, 1H) 7.07 (t, 1H), 7.00 (t, 1H), 4.80-  
 15 4.78 (m, 1H), 4.59-4.54 (m, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.34 (dd, J=5.4  
 Hz, 14.9 Hz, 1H), 3.15 (dd, J=9.5 Hz, 14.7 Hz, 1H), 2.59-2.44 (m, 2H),  
 2.14-2.08 (m, 1H), 2.06 (s, 3H), 2.02-1.94 (m, 3H), 1.54 (s, 3H), 1.31 (s,  
 3H), 1.25 (t, J=7.1 Hz, 3H).

20

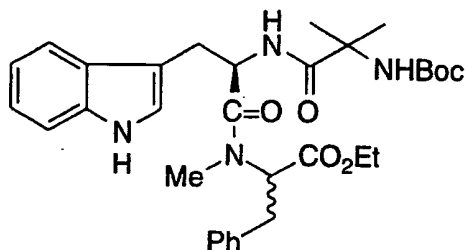
EXAMPLE 7

25

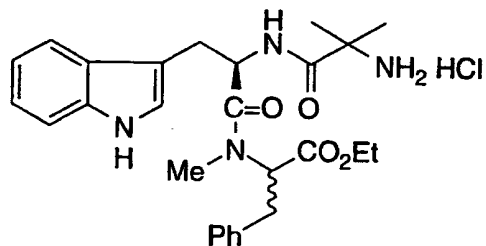


30

- 58 -

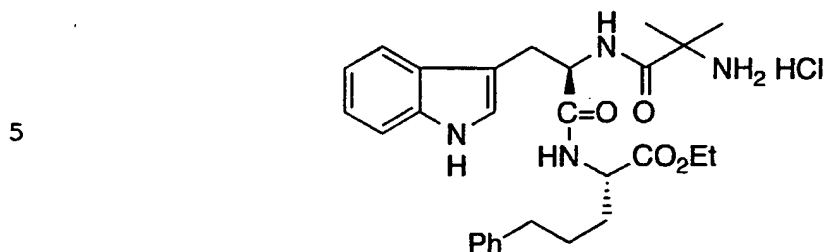
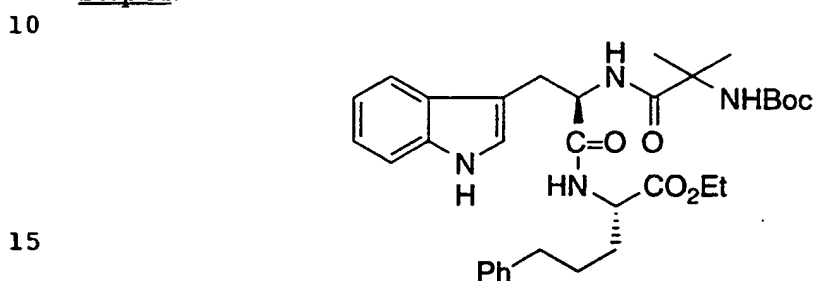
Step A:

Prepared by the procedure described in Example 1, Step B from N-methyl-DL-phenylalanine ethyl ester hydrochloride (125 mg, 0.514 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 141 mg. FAB-MS calc. for C<sub>32</sub>H<sub>42</sub>N<sub>4</sub>O<sub>6</sub>: 578; found: 579 (M+H).

Step B:

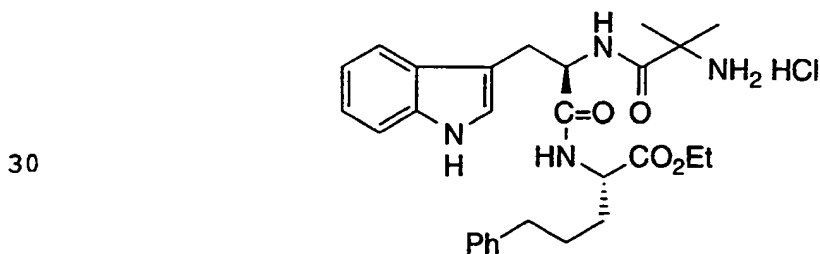
Prepared by the procedure described in Example 1, Step C. The intermediate from previous step (90 mg) and HCl gas in ethyl acetate (5 mL) at 0°C. Product: 78 mg. FAB-MS calc. for C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>: 478; found: 479 (M+H).

- 59 -

EXAMPLE 8Step A:

Prepared by the procedure described in Example 1, Step B from L-2-amino-5-phenylpentanoic acid ethyl ester hydrochloride (Chenault et al, *J. Am. Chem. Soc.*, 111, 6354-6364 (1989)) (200 mg, 0.776 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.02 mmol). Product: 265.4 mg. FAB-MS calc. for C<sub>33</sub>H<sub>44</sub>N<sub>4</sub>O<sub>6</sub>: 592; found: 593 (M+H).

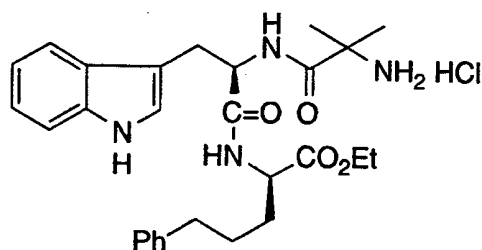
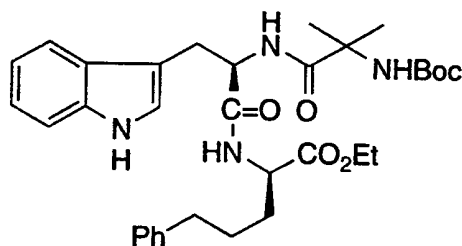
25

Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (235 mg) and HCl gas in ethyl

- 60 -

acetate (5 mL) at 0°C. Product: 210 mg. FAB-MS calc. for  $C_{28}H_{36}N_4O_4$ : 492; found: 493 (M+H).  $^1H$ NMR (400 MHz,  $CD_3OD$ ): 7.61 (d,  $J=8.7$  Hz, 1H), 7.29-6.99 (m, 9H), 4.79 (t,  $J=7.5$  Hz, 1H), 4.23 (dd,  $J=5$  Hz, 8.3 Hz, 1H), 4.13-4.08 (m, 2 H), 3.27 (dd,  $J=7$  Hz, 14 Hz, 1H), 3.12 (dd,  $J=8$  Hz, 14 Hz, 1H), 2.51-2.46 (m, 2H), 1.63-1.54 (m, 1H), 1.54 (s, 3H), 1.50-1.40 (m, 1H), 1.37 (s, 3H), 1.40-1.20 (m, 2H), 1.20 (t,  $J=7.1$  Hz, 3H).

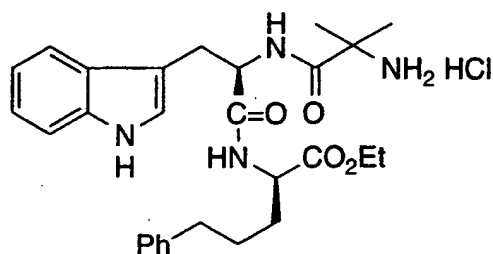
EXAMPLE 9Step A:

Prepared by the procedure described in Example 1, Step B from D-2-amino-5-phenylpentanoic acid ethyl ester hydrochloride (Chenault et al, *J. Am. Chem. Soc.*, **111**, 6354-6364 (1989)) (200 mg, 0.776 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.02 mmol). Product: 260.0 mg. FAB-MS calc. for  $C_{33}H_{44}N_4O_6$ : 592; found: 593 (M+H).

- 61 -

Step B:

5

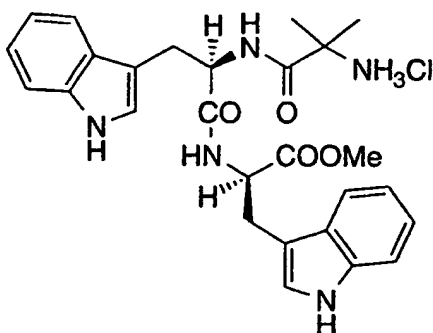


Prepared by the procedure described in Example 1, Step C.

10 The intermediate from previous step (230 mg) and HCl gas in ethyl acetate (5 mL) at 0°C. Reaction time: 30 minutes. Yield: 201 mg  
 FAB-MS calc. for C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub>: 492; found: 493 (M+H).  
<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): 7.65 (d, J=7.8 Hz, 1H), 7.32-6.98 (m, 9H),  
 4.84-4.80 (m, 1H), 4.39 (dd, J=5 Hz, 8 Hz, 1H), 4.13 (q, J=7.1 Hz, 2H),  
 15 3.33 (dd, J=5.4 Hz, 15 Hz, 1H), 3.12 (dd, J=9.6 Hz, 14.5 Hz, 1H), 2.70-  
 2.60 (m, 2H), 1.90-1.80 (m, 1H), 1.75-1.60 (m, 3H), 1.50 (s, 3H), 1.27 (s,  
 3H), 1.23 (t, J=7.1 Hz, 3H).

EXAMPLE 10

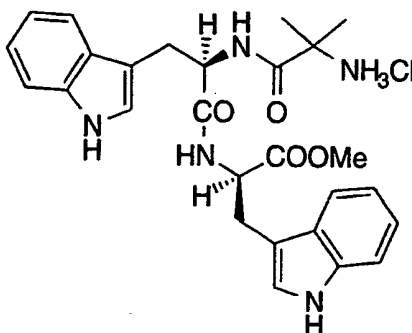
20



25

30

- 62 -

Step A:

To a solution of 0.10g of Intermediate 1 in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added 0.10g of D-TRP methyl ester, 64 mg of HOBT, 0.052 mL of NMM, and 0.10g of EDC and stirred at RT for 18h. The reaction mixture was diluted with 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with 0.10N HCl (10 mL), saturated NaHCO<sub>3</sub> (10 mL), dried over MgSO<sub>4</sub> and concentrated. Flash chromatography of the residue with CH<sub>2</sub>Cl<sub>2</sub>-acetone (1:1) as the eluent gave 0.134g of the desired material.

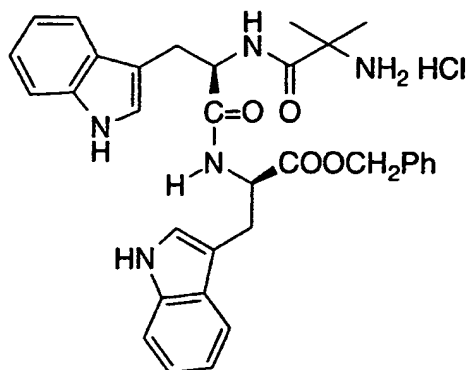
To a solution of this above intermediate in 5 mL of ethyl acetate at 0°C was bubbled in HCl gas for 30 seconds. The flask was capped and stirred for 30 minutes. Ether was added and the precipitate was filtered under an N<sub>2</sub> atmosphere. This gave 89 mg of the title compound as a yellow solid.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.60 (d, 1H), 7.42 (d, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.97-7.10 (m, 6H), 4.78 (dd, 1H), 4.70 (dd, 1H), 3.68 (s, 3H), 3.30-3.10 (m, 4H), 1.40 (s, 3H), 1.28 (s, 3H).

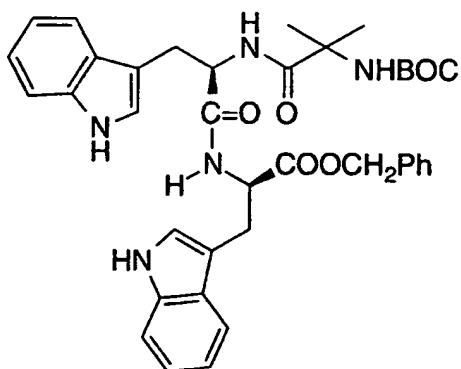


- 63 -

### EXAMPLE 10A

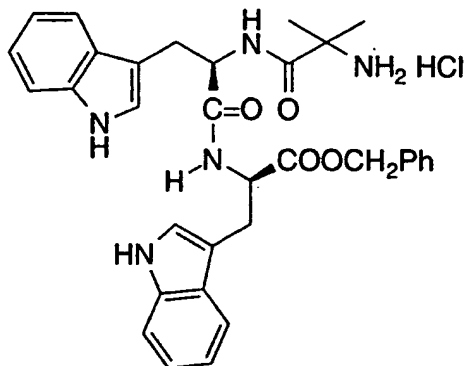


**Step A:**



The above intermediate was synthesized as described in Example 10 but D-Tryptophan benzyl ester was used in place of the methyl ester.

**Step B:**

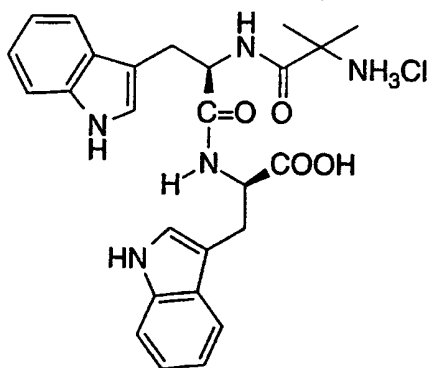


- 64 -

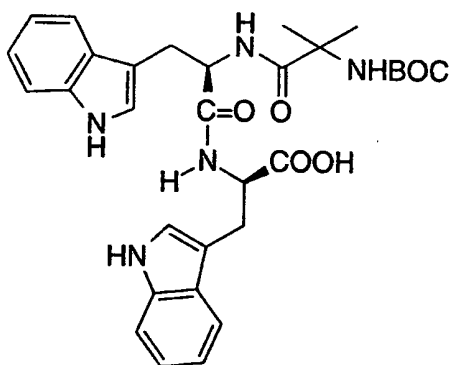
A solution of 0.075g of the intermediate synthesized in Step A in ethyl acetate was treated with HCl (gas) at 0°C for a few seconds. After 30 min. ether was added and the precipitate was filtered under a nitrogen atmosphere and dried to give 0.060g of the title compound as a pale yellow solid.

<sup>1</sup>H NMR (400MHz; CD<sub>3</sub>OD) 8.15, 7.83, 7.60, 7.47 (4 doublets, 2H), 7.38-6.90 (m, 13H), 5.00 (ABq, 2H), 4.80-4.65 (m, 2H), 3.30-3.06 (m, 4H), 1.40 (s, 3H), 1.22 (s, 3H).

#### EXAMPLE 10B

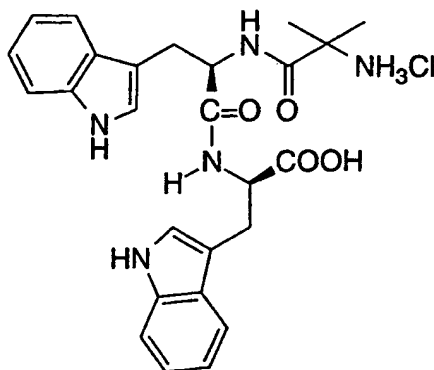


#### Step A:



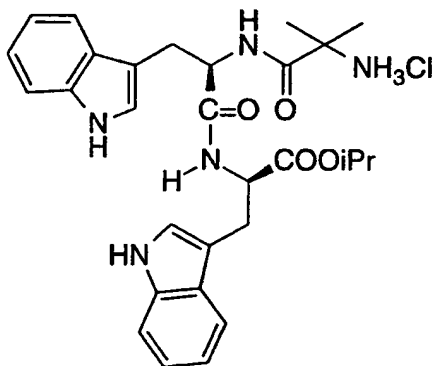
A solution of 0.70g of the compound prepared in Step A of Example 10A was hydrogenated with 10% Pd/C in methanol for 3h. The catalyst was filtered off through a pad of celite. The filtrate was concentrated to give the desired acid as a white foam.

- 65 -

Step B:

The intermediate prepared in Step A was deprotected with the HCl/EtOAc protocol as described above to give the title compound as an off-white solid.

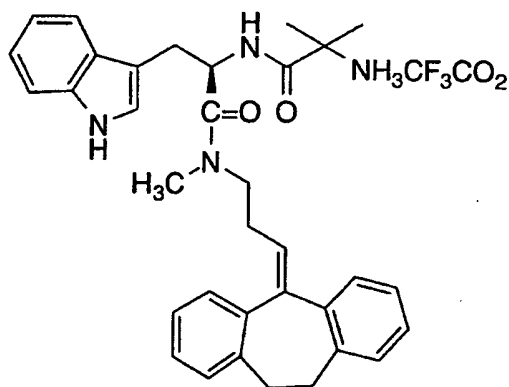
$^1\text{H}$  NMR (400MHz;  $\text{CD}_3\text{OD}$ ) 7.92, 7.74, 7.60, 7.30 (4 doublets, 2H), 7.30 (d, 2H), 7.16-6.90 (m, 8H), 4.81-4.65 (m, 2H), 3.34-3.06 (m, 4H), 1.38 (s, 3H), 1.22 (s, 3H).

EXAMPLE 10C

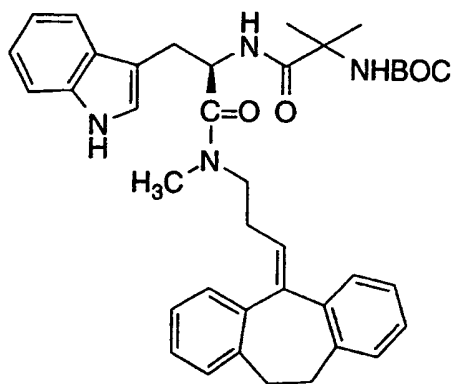
A solution of 0.10g of the intermediate prepared in Step A of Example 10B in isopropanol was treated with HCl(gas) at  $0^\circ\text{C}$  for 10 seconds. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude precipitate was washed with EtOAc- $\text{CH}_2\text{Cl}_2$ -MeOH-ether (2:1:0.10:2) and the remaining solid was collected and dried to give the title compound.

<sup>1</sup>H NMR (400MHz; CD<sub>3</sub>OD) 8.15, 7.80, 7.62, 7.45 (4 doublets, 2H), 7.30 (d, 2H), 7.16-6.95 (m, 8H), 4.90 (m, 1H), 4.80-4.60 (m, 2H), 3.30-3.06 (m, 4H), 1.40 (s, 3H), 1.25 (s, 3H), 1.20 and 1.05 (2 doublets, 6H).

**EXAMPLE 10D**



**Step A:**

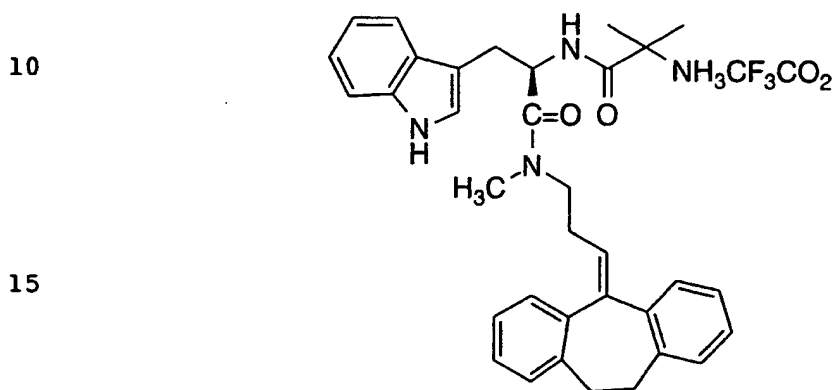


To a solution of 0.10g of N-tBOC-D-Tryptophan in 10mL of chloroform was added 0.090g of the monomethylamine derivative of amitriptyline, 0.055g of HOBT and 0.086g of EDC and stirred at RT for 2h. The reaction was diluted with 15mL of ether and washed with water (5mL), 10% aqueous citric acid (10mL), and saturated aqueous NaHCO<sub>3</sub> (5mL), dried over anhydrous MgSO<sub>4</sub> and concentrated to provide a crude product that was used without purification.

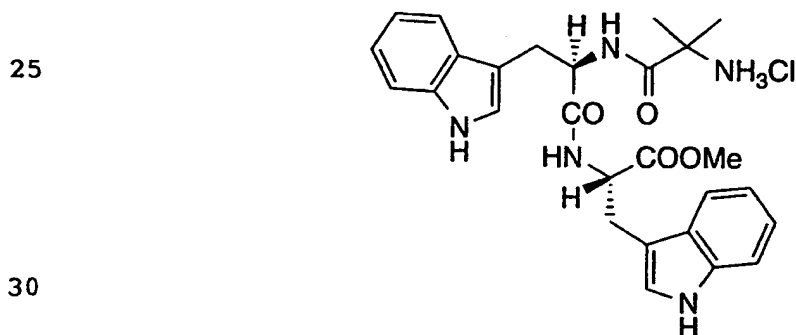
A solution of crude product from above was treated with 3mL of TFA and 4 drops of anisole for 1h at RT. The reaction mixture was evaporated to dryness and azeotroped with toluene. The residue was

- 67 -

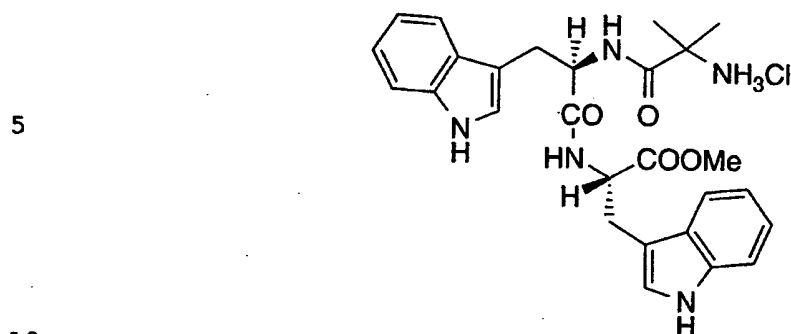
dissolved in 5mL of chloroform and reacted with 0.076g of N-BOC-a-methylalanine in the presence of 0.055g of HOBT, 0.15mL of N-methylmorpholine, and 0.086g of EDC for 2h. The reaction mixture was worked-up as described above and the crude product was separated by  
5 flash chromatography (10g silica gel; hexane-EtOAc (2:1) as eluent) gave 0.069g of the desired product.

Step B:

The compound prepared in Step A (0.069g) was treated with 1.0mL of TFA for 1h. The reaction mixture was evaporated to dryness to  
20 give 0.052g of the desired product after trituration with ether.

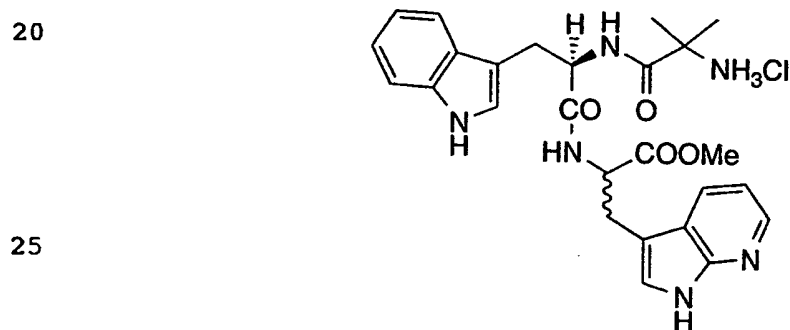
EXAMPLE 11

- 68 -

Step A:

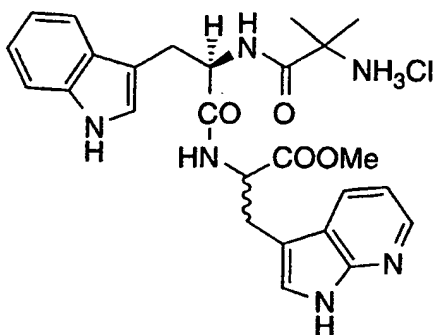
This compound was made in a similar manner to the compound reported in Example 10 but L-TRP methyl ester was used in place of D-TRP methyl ester.

15  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7.60 (d, 1H), 7.42 (d, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.97-7.10 (m, 6H), 4.78 (dd, 1H), 4.70 (dd, 1H), 3.68 (s, 3H), 3.30-3.10 (m, 4H), 1.40 (s, 3H), 1.28 (s, 3H).

EXAMPLE 12

30

- 69 -

Step A:

To 0.40g of commercially available (DL)-7-aza-TRP in 10 mL of dry ethanol at 0°C was bubbled in HCl gas for 15 seconds. The reaction mixture was heated to reflux for 18h. The reaction mixture was neutralized with aqueous Na<sub>2</sub>CO<sub>3</sub> solution, and extracted with CH<sub>2</sub>Cl<sub>2</sub>.

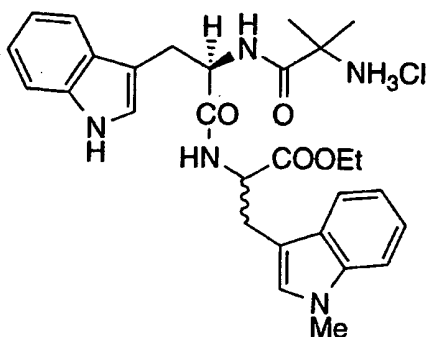
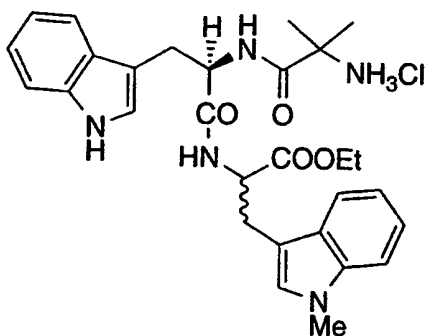
The combined organic extracts were washed with brine, dried over K<sub>2</sub>CO<sub>3</sub>, and concentrated.

To 0.10g of the above ethyl ester in 4 mL of CH<sub>2</sub>Cl<sub>2</sub> was added 0.10g of Intermediate 1, 0.069g of HOBT, 0.12g of EDC and stirred at RT for 2 days. The reaction mixture was poured in saturated aqueous NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatography of the residue with CH<sub>2</sub>Cl<sub>2</sub>-acetone-ether (3:2:1) as the eluent gave 75 mg of the title compound.

To 75 mg of the above intermediate in 2 mL of ethyl acetate was bubbled in HCl gas for 15 seconds. The flask was capped and stirred for 30 minutes. Ether was added and the precipitate was filtered under an N<sub>2</sub> atmosphere to give the title compound as a yellow solid.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.75 (d, 1H), 8.40 (d, 1H), 7.70-7.55 (m, 3H), 7.30 (d, 1H), 7.15-6.93 (m, 3H), 4.80-4.66 (m, 2H), 4.10 (2q, 2H), 3.30-3.10 (m, 4H), 1.52 (s, 3H), 1.36 (s, 3H), 1.18 (2t, 3H).

- 70 -

EXAMPLE 13Step A:

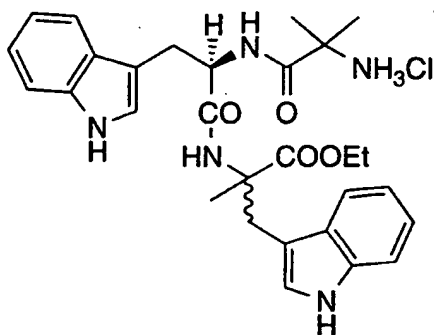
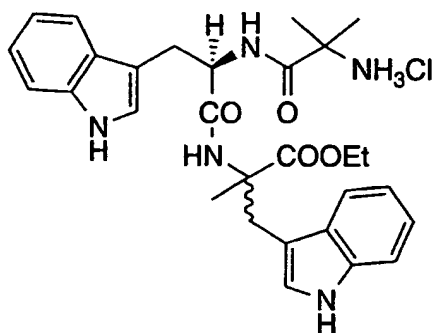
This compound was made as described in Step A of Example 11 but (DL)-1-methyl TRP was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.10-8.00 (2d, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.33 (d, 1H), 7.31 (d, 1H), 7.18-7.05 (m, 3H), 7.03-6.95 (m, 3H), 4.80-4.70 (m, 1H), 4.70-4.60 (m, 1H), 4.05 (2q, 2H), 3.70 (s, 3H), 3.28-3.00 (m, 4H), 1.44 (s, 3H), 1.26 (s, 3H), 1.13 (t, 3H).



- 71 -

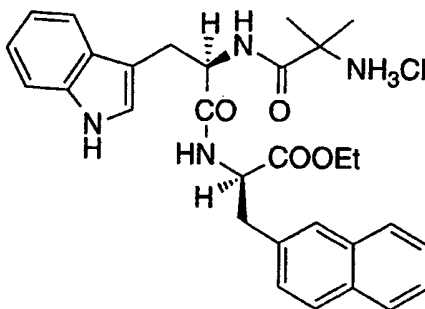
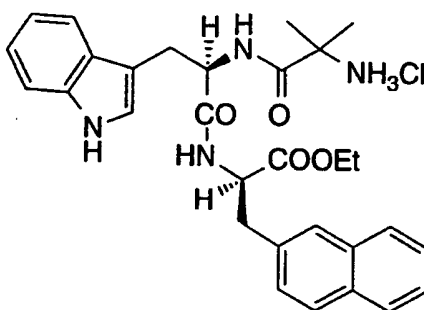
EXAMPLE 14Step A:

This compound was made as described in Step A of Example 11 but (DL)- $\alpha$ -methyl TRP was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.05 (s, 1/2H), 7.98 (d, 1/2H), 7.90 (d, 1/2H), 7.85 (s, 1/2H), 7.63 (t, 1H), 7.48 (t, 1H), 7.33 (d, 2H), 7.13-6.98 (m, 4H), 4.82-4.70 (m, 1H), 4.10 (2q, 2H), 3.43-2.20 (m, 3H), 3.15-3.00 (m, 1H), 1.50 and 1.49 (2s, 6H), 1.41 (s, 1H), 1.30-1.14 (m, 5H).

- 72 -

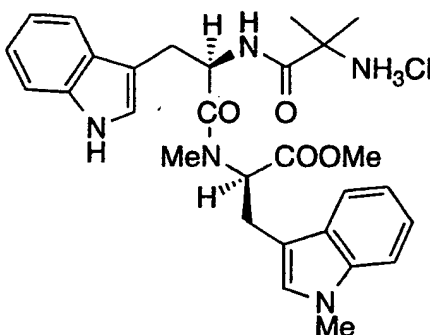
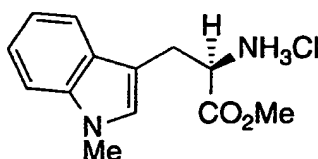
EXAMPLE 15Step A:

This compound was made as described in Step A of Example 11 but (D)-2-naphthyl alanine was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.33 (d, 1H), 7.80-7.75 (m, 3H), 7.66 (s, 1H), 7.60 (d, 1H), 7.48-7.39 (m, 2H), 7.35 (dd, 1H), 7.31 (d, 1H), 7.08 (t, 1H), 6.98 (t, 1H), 5.50 (s, 1H), 4.80-4.70 (m, 1H), 4.10 (q, 1H), 3.15-3.08 (m, 4H), 1.40 (s, 1H), 1.28 (s, 3H), 1.15 (t, 3H).

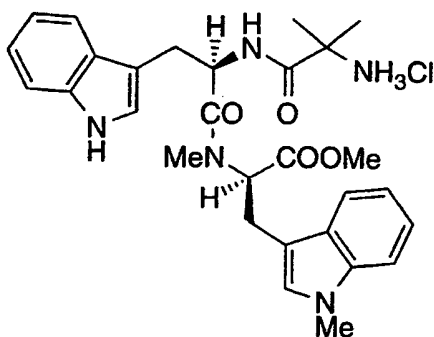
- 73 -

EXAMPLE 16Step A:

To a suspension of 0.55g of 60% sodium hydride in mineral oil in 40 mL of dry DMF at 0°C was added a solution of 1.0g of N-*t*-BOC-D-TRP in 10 mL of DMF and stirred for 30 min. Methyl iodide (1 mL) was added and stirred at RT for 1h. The reaction mixture was poured into ice-water and extracted with CHCl<sub>3</sub>. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. This material was dissolved in 5 mL of methanol and 0.50 mL of concentrated HCl was added and heated at reflux for 24h. The reaction mixture was concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with aqueous NaHCO<sub>3</sub>. The aqueous layers were back extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried over K<sub>2</sub>CO<sub>3</sub>, and concentrated.

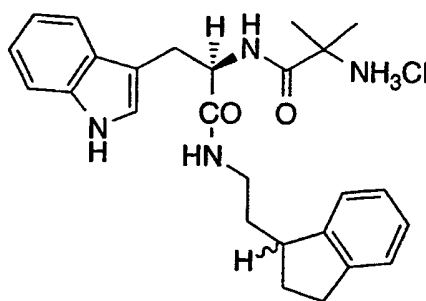
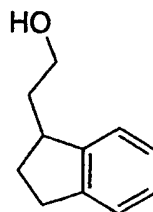
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.60 (d, 1H), 7.28 (d, 1H), 7.22 (t, 1H), 7.10 (t, 1H), 6.89 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.53 (t, 1H), 3.16 (dd, 1H), 3.09 (dd, 1H), 2.37 (s, 3H).

- 74 -

Step B:

The above intermediate was transformed to the title compound as described in Step A of Example RN-3 but the intermediate from Step A was used in place of (DL)-7-aza TRP.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7.58 (d, 1H), 7.35 (d, 1H), 7.32-7.25 (m, 2H), 7.15 (t, 1H), 7.10-6.95 (m, 4H), 6.88 (s, 1H), 5.34 (dd, 1H), 5.03 (t, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.38 (dd, 1H), 3.22-3.10 (m, 2H), 2.96 (s, 3H), 2.58 (bd, 1H), 1.50 (s, 3H), 1.28 (s, 3H).

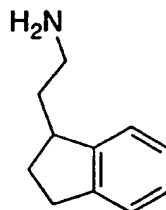
EXAMPLE 17Step A:

- 75 -

To 1.0g of indene in 10 mL of dry THF at -78°C was added 10.3 mL of 1.6M n-BuLi in hexane and stirred for 45 minutes. A solution of 2.50g of 2-*t*-butyldimethylsilyloxy-1-bromoethane in 10 mL of THF was added and allowed to warm up to 0°C and stir for 6h. The reaction mixture was poured into 50 mL of water and extracted with ether (3X50 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, and concentrated to 8.6g of a product. This material was stirred overnight in 50 mL of THF and 50 mL of 5% aqueous HCl. The reaction was extracted with ether (2X50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO<sub>4</sub> and concentrated to yield 4.6g of the crude product. Flash chromatography of this residue with hexane-ether (1:1) as eluent gave 4.6g of product.

This material was dissolved in 25 mL of ethanol and 1.0g of 10% Pd/C was added and hydrogenated for 3h. The catalyst was filtered off through a pad of celite and washed with ether, and concentrated to give a colorless oil. This material was used without purification.

Step B:



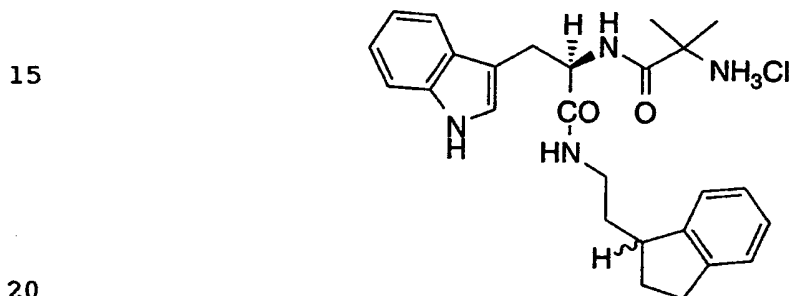
To 0.471g of the above intermediate in 10 mL of THF at 0°C was added 0.61 mL of triethylamine and 0.27 mL of mesyl chloride and stirred for 1h. The reaction mixture was poured into 10 mL of saturated aqueous NaHCO<sub>3</sub> and extracted with ether (2X10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated. To this crude product in 5 mL of DMSO was added 0.50 g of sodium azide and stirred at 60°C overnight. The reaction mixture was poured into 15 mL of water and extracted with ether (2X15 mL). The combined organic extracts were washed with brine (10 mL),

- 76 -

dried over  $\text{MgSO}_4$ , and concentrated to give a the azido-material as a brown oil.

Nickel/aluminum alloy was added to a solution of the above intermediate in 10 mL of ethanol and 10 mL of 20% aqueous NaOH solution and stirred at  $60^\circ\text{C}$  for 1h. The reaction mixture was cooled to RT, the solids were filtered and washed with  $\text{CHCl}_3$ . The filtrate was concentrated, and then diluted with 10 mL of brine, and extracted with  $\text{CHCl}_3$  (2X10 mL). The combined organic extracts were washed with brine (10 mL), dried over  $\text{K}_2\text{CO}_3$ , and concentrated. This gave 0.150g of the amine.

Step C:



To a solution of 0.150g of the amine intermediate from Step B in 10 mL of  $\text{CHCl}_3$  was added 0.28g of *N*-*t*-BOC-D-TRP, 0.142g of HOBT, and 0.220g of EDC and stirred at RT for 3h. The reaction mixture was poured into 10 mL of water and extracted with ether (2X15 mL). The combined organic extracts were extracted with 20% aqueous citric acid (10 mL), saturated  $\text{NaHCO}_3$  (10 mL), dried over  $\text{MgSO}_4$ , and concentrated. The residue was treated with 3 mL of  $\text{CH}_2\text{Cl}_2$ , 3 mL of TFA, and 0.10 mL of anisole for 1h. The reaction mixture was evaporated to dryness and the residue was azeotroped with toluene, dried under vacuum, and used without purification. To a solution of this material in 10 mL of  $\text{CHCl}_3$  was added 0.70 mL of NMM, 0.142g of HOBT, 0.212g of *N*-*t*-BOC- $\alpha$ -methylalanine, and stirred at RT for 3h. The reaction was worked-up as described above. Flash chromatography

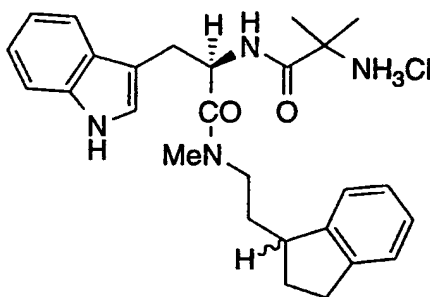
- 77 -

of the residue with hexane-ethyl acetate (1:1) as the eluent gave 86 mg of the desired product.

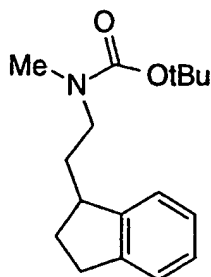
Deprotection of the intermediate with TFA (2 mL), in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), with 0.020 mL of anisole, gave the title compound as a solid. This material is a mixture of diastereomers.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.60 (d, 1H), 7.55-7.50 (m, 1H), 7.29 (dd, 1H), 7.18-6.95 (m, 6H), 4.60 (t, 1H), 3.30-3.10 (m, 4H), 2.95-2.70 (m, 3H), 2.20 (q, 1H), 1.81 (q, 1H), 1.66-1.53 (m, 1H), 1.50 (s, 3H), 1.42-1.30 (m, 1H), 1.33 (s, 3H).

#### EXAMPLE 18



#### Step A:



To 80 mg of the amine intermediate prepared in Step B of Example 17 in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and 0.10 mL of triethylamine was added 0.104g of di-*t*-butyl dicarbonate and stirred for 2 h. The reaction mixture poured into 5 mL of 20% aqueous citric acid and extracted with ether (2X10 mL). The combined organic extracts were washed with saturated

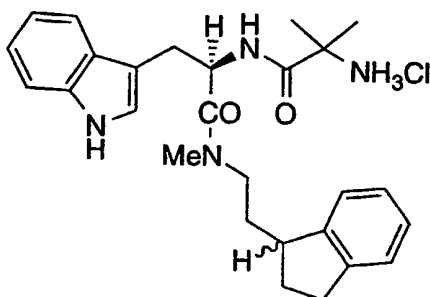
- 78 -

aqueous NaHCO<sub>3</sub>, brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated. This gave 0.123g of the desired product.

To a solution of the above intermediate in 5 mL of THF was added 1.50 mL of 1M solution of sodium bis(trimethylsilyl)amide in THF at 0°C, and stirred for 30 minutes. Methyl iodide (0.10 mL) was added and stirred at RT overnight. The reaction mixture was poured into water (10 mL), and extracted with ether (3X10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated to give 0.108g of the methylated product.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.30-7.05 (m, 4H), 3.45-3.20 (m, 2H), 3.20-3.00 (m, 1H), 3.00-2.75 (m, 1H), 2.88 (s, 1H), 2.33 (q, 1H), 2.10 (q, 1H), 1.80-1.55 (m, 2H), 1.48 (s, 9H), 1.50-1.35 (m, 1H).

Step B:

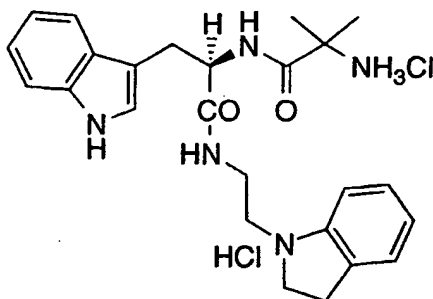
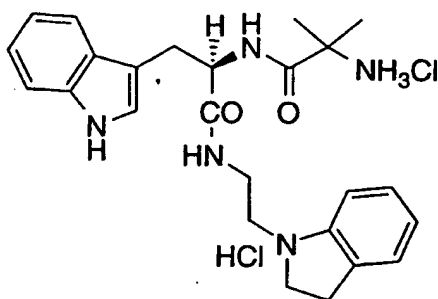


The intermediate was deprotected with TFA and then transformed to the title compound as described in Step C of Example 17. This compound is a mixture of diastereomers.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.65-7.50 (m, 1H), 7.40-7.20 (m, 1H), 7.20-6.5 (m, 7H), 5.20-5.05 (m, 1H), 3.40-3.00 (m, 4H), 3.00-2.60 (m, 5H), 2.25 (q, 1/2H), 2.10-1.95 (m, 1/2H), 1.90-1.78 (m, 1H), 1.75-1.30 (m, 10H).



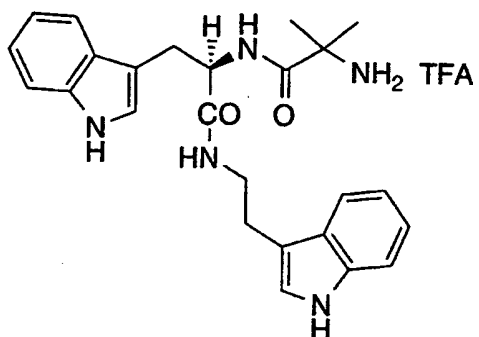
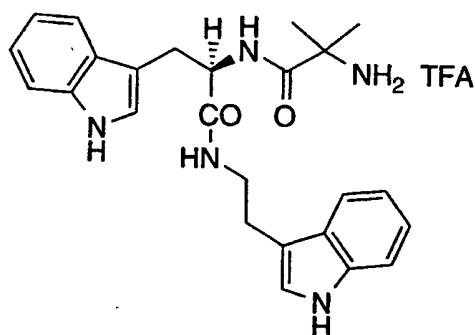
- 79 -

EXAMPLE 19Step A:

The indoline ethanol was converted to the indoline ethyl amine as described in Step B of Example 17. The amine derivative thereby synthesized was converted to the title compound as described in Step C of Example 17 with one minor modification. The final deprotection was carried out in methanol with concentrated HCl to give the dihydrochloride salt.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.20 (d, 1H), 7.60 (d, 1H), 7.55-7.40 (m, 4H), 7.28 (d, 1H), 7.17 (s, 1H), 7.00-6.90 (m, 2H), 4.70-4.60 (m, 1H), 3.95-3.85 (m, 1H), 3.82-3.70 (m, 1H), 3.60-3.45 (m, 2H), 4.40-3.15 (m, 4H), 1.60 (m, 3H), 1.36 (m, 3H).

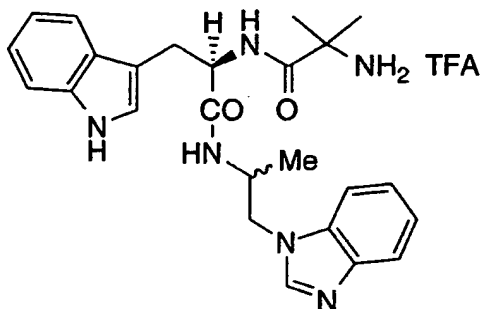
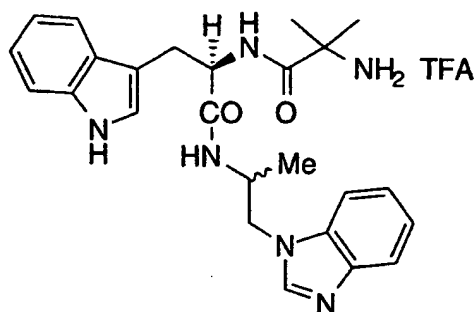
- 80 -

EXAMPLE 20Step A:

The title compound was prepared from commercially available N-*t*-BOC-D-tryptophan and tryptamine as described in Step C of Example 17. The title compound was isolated as a free base after NaHCO<sub>3</sub> work-up of the final trifluoroacetic acid salt.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.60 (d, 1H), 7.40 (d, 1H), 7.32 (d, 1H), 7.27 (d, 1H), 7.10-6.90 (m, 6H), 4.52 (t, 1H), 3.50-3.30 (m, 2H), 3.18 (t, 2H), 2.70 (t, 3H), 1.13 (s, 6H).

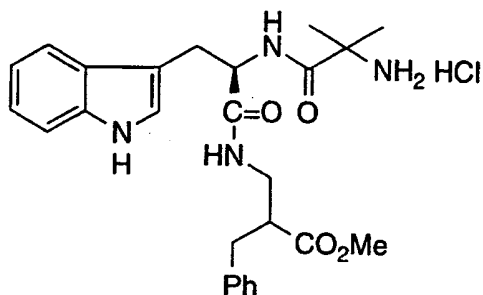
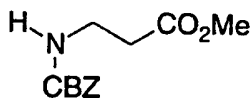
- 81 -

EXAMPLE 21Step A:

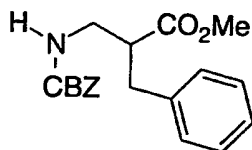
The title compound was synthesized from 1-(benzimidazol-yl)-2-propylamine and N-*t*-BOC-D-TRP as described in Step C Example 17. This compound is a mixture of diastereomers.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.609.22 and 9.15 (2s, 1H), 8.30 and 8.10 (2d, 1H), 8.00-7.80 (m, 2H), 7.70-7.60 (m, 2H), 7.50 (dd, 1H), 7.31 (t, 1H), 7.15-6.93 (m, 4H), 4.60-4.10 (m, 3H), 3.10 (d, 1H), 2.88 (d, 1H), 2.83-2.67 (m, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.30 and 0.75 (2d, 3H).

- 82 -

EXAMPLE 2210 Step A:15 N-CBZ-β-alanine methyl ester

Prepared by the procedure described in Example 1, Step A from N-CBZ-β-alanine (5g, 22.4 mmole), methanol and thionyl chloride to give the title compound.

20 Step B:

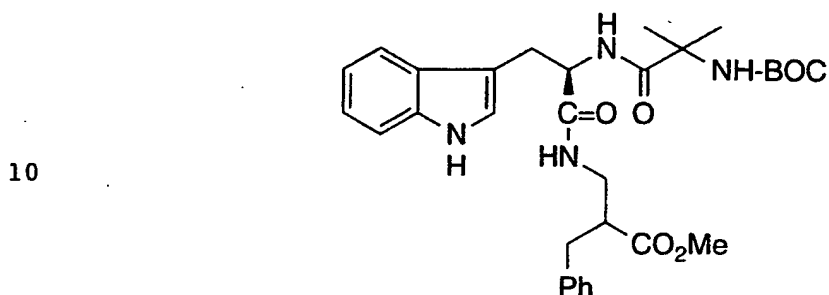
25

To a stirred solution of the intermediate (330 mg) from the previous step in THF (3 mL) was added potassium bis(trimethylsilyl)amide (3 mL, 0.5 M in toluene) at -78°C followed by the addition of hexamethylphosphoramide (5 mL). This mixture was warmed to room temperature to give a clear solution and then re-cooled to -78°C. To this solution was added another portion of potassium bis(trimethylsilyl)amide (3 mL, 0.5N in toluene). After 1 hour at -78°C, benzyl bromide (193 μL) was added to reaction mixture. The solution was stirred at -78°C for 3 hours and poured into 0.5N HCl, extracted with ether three times. The combined organic layers were washed with water (five times), brine,

- 83 -

dried over magnesium sulfate, and concentrated. The residue was purified by Pre-TLC (hexanes/ethyl acetate=4/1) to give the desired compound (164 mg, 35% yield).

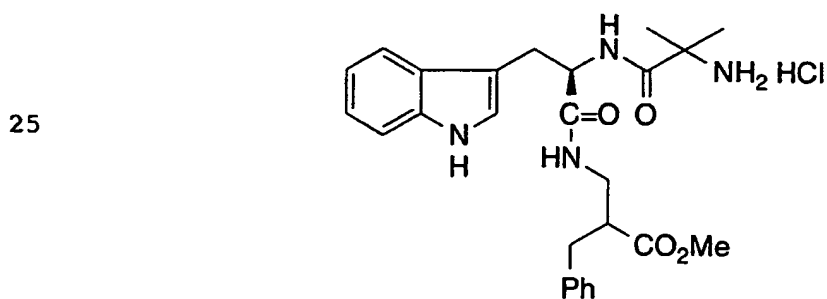
5 Step C:



15 To a solution of the intermediate (154 mg) obtained from the previous step in methanol was added Pd(OH)<sub>2</sub> and hydrogenated under H<sub>2</sub> balloon for 1/2 hour. The mixture was filtered through Celite. The filtrate was concentrated. The residue was coupled to the Intermediate 1 by the procedure described in Example 1, Step B (without NMM) to give desired compound (240 mg, 87%).

20

Step D:



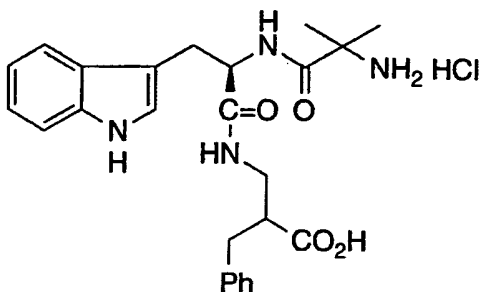
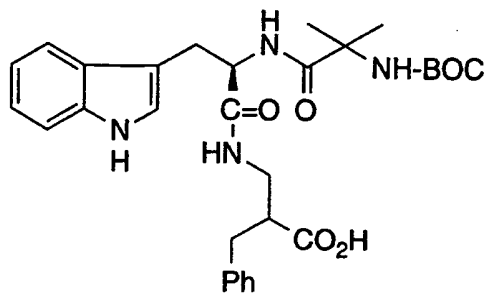
30

Prepared from the intermediate obtained from the previous step (31 mg) HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the title compound (27 mg).

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, mixture of two diastereomers): 7.61 (m, 1 H), 7.32-6.99 (m, 9 H), 4.70 (m, 1 H), 3.56 (s, 3/2 H), 3.54 (s, 3/2 H),

- 84 -

3.37 (m, 1 H), 3.26 (m, 2 H), 3.10 (m, 1 H), 2.74 (m, 3 H), 1.54 (s, 3 H),  
1.34 (s, 3/2 H), 1.32 (s, 3/2 H).

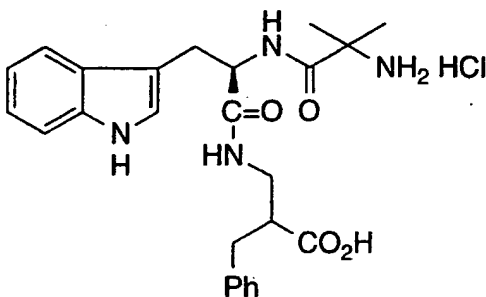
EXAMPLE 23Step A:

To a stirred solution of the intermediate from Example 22, Step C (66 mg) in 1 mL of methanol was added lithium hydroxide (25 mg) in 1 mL of water. The reaction was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was diluted with water and acidified with 1N hydrochloric acid and then extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired compound (44 mg).

- 85 -

Step B:

5



10

Prepared from the intermediate obtained from the previous step (7 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (5 mg).

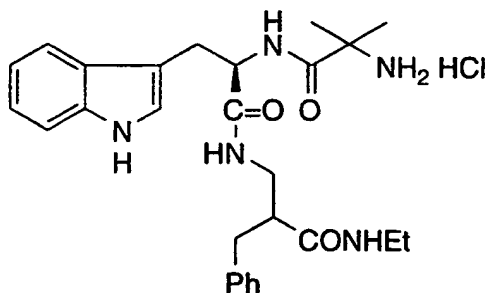
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, mixture of two diastereomers): 7.62 (d, 8 Hz, 1 H), 7.31-6.99 (m, 9 H), 4.71 (m, 1 H), 3.37 (m, 1 H), 3.28 (m, 2 H), 3.12 (m, 1 H), 2.77 (m, 3 H), 1.53 (s, 3 H), 1.30 (s, 3 H).

15

FAB-MS: 451.2 (M+1).

EXAMPLE 24

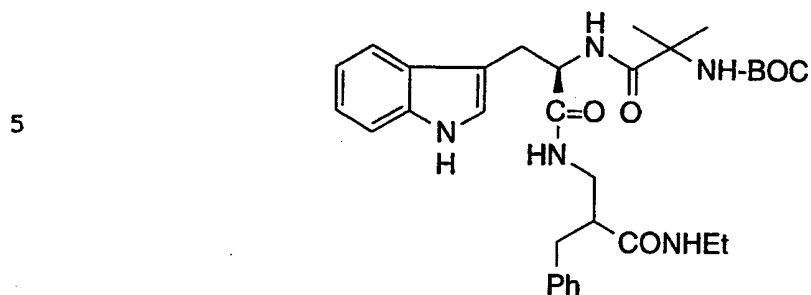
20



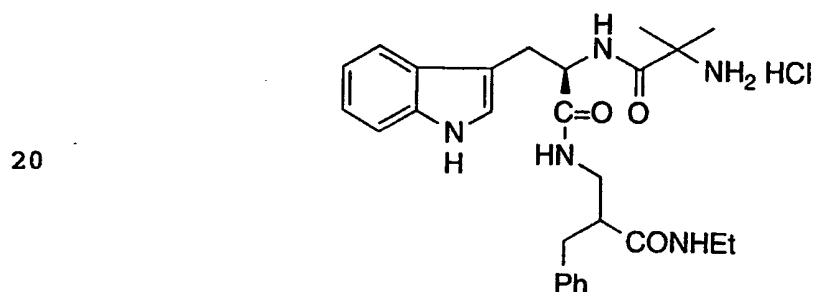
25

30

- 86 -

Step A:

Prepared from the intermediate from Example 23, Step A (37 mg) and ethylamine hydrochloride (16 mg) by the procedure described in Example 1, Step C using triethylamine instead of NMM to give the coupling product.

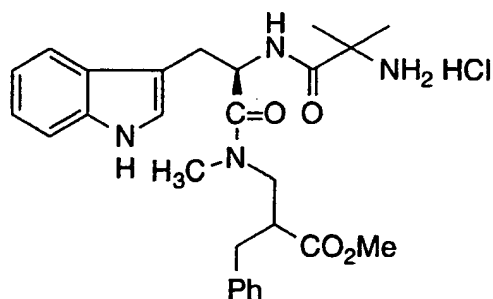
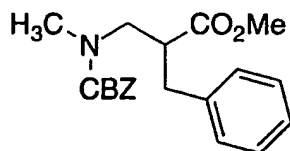
15 Step B:

Prepared from the intermediate from the previous step and HCl gas at 0°C by the procedure described in Example 1, Step C to give the desired compound (24 mg).

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, mixture of two diastereomers): 7.62 (d, 8 Hz, 1 H), 7.31-6.99 (m, 9 H), 4.68 (m, 1 H), 3.37-3.23 (m, 3 H), 3.15-2.91 (m, 3 H), 2.65 (m, 3 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 0.90 (m, 3 H).  
 30 FAB-MS: 478.3 (M+1).



- 87 -

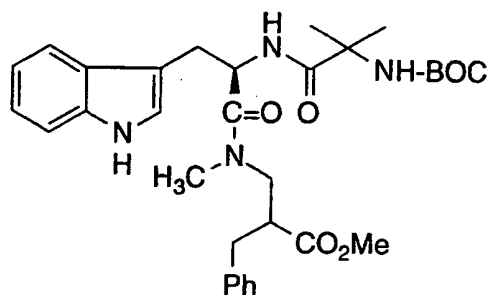
EXAMPLE 2510 Step A:

15

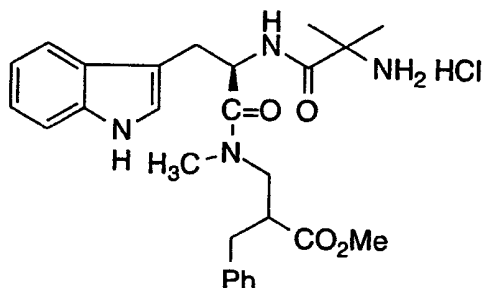
To a solution of the intermediate obtained from Example 22, Step A (1.15 g) in 10 mL of THF was added potassium bis(trimethylsilyl)amide (10.7 mL, 0.5N in toluene) at -78°C and then warmed to room temperature. To this reaction mixture was added hexamethylphosphoramide (10 mL) to give a clear solution and then re-cooled to -78°C. This solution was added another portion of potassium bis(trimethylsilyl)amide (10.7 mL, 0.5N in toluene). After 1 hour at -78°C, benzyl bromide (577  $\mu$ L) was added to reaction mixture. The solution was stirred at -78°C for 4 hours and quenched with 1 mL of methyl iodide. The mixture was poured into 1N HCl, extracted with ether three times. The combined organic layers were washed with water (five times), brine, dried over magnesium sulfate, and concentrated. The residue was purified on silica gel to give the desired compound (1.43 g, 90%).

30

- 88 -

Step B:

Prepared from the intermediate from the previous step (757 mg) by the procedure described in Example 22, Step C to give the coupling product (806 mg, 60%).

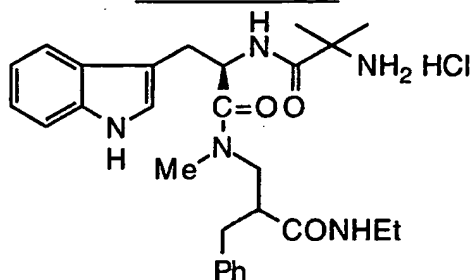
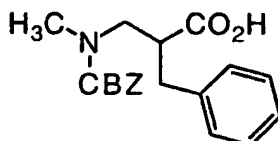
Step C:

Prepared from the intermediate from the previous step (30 mg) by the procedure described in Example 1, Step C to give the desired compound 24 mg.

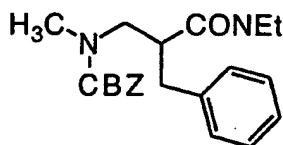
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, mixture of two diastereomers): 7.56 (m, 1 H), 7.32-6.89 (m, 9 H), 5.12 (m, 1 H), 3.53 (s, 3/2 H), 3.48 (s, 3/2 H), 3.42 (m, 1 H), 3.18 (m, 2 H), 2.99 (m, 1 H), 2.85 (s, 3 H), 2.70 (m, 3 H), 1.55 (s, 3 H), 1.45 (s, 3/2 H), 1.42 (s, 3/2 H).

FAB-MS: 479.3 (M+1).

- 89 -

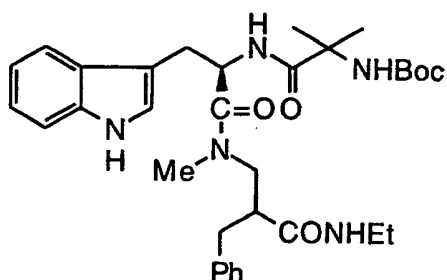
EXAMPLE 26Step A:

To a solution of the intermediate obtained from Example 25, Step A (304 mg) in 2 ml of methanol was added 2 ml 6N sodium hydroxide. The reaction was stirred at room temperature for 2 hours. This basic mixture was washed with ether three times. The ether layer was then washed with 1N sodium hydroxide three times. The combined basic aqueous layers were cooled to 0°C and acidified with conc. HCl until a precipitate formed. Litmus paper turns blue to red. This solution was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give the desired compound (225 mg, 75 %).

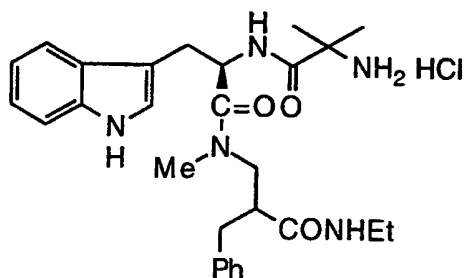
Step B:

Prepared from the intermediate from the previous step (32 mg) and ethyl amine hydrochloride by the procedure described in Example 1, Step B using triethyl amine instead of NMM to give the coupling product (24 mg, 67%).

- 90 -

Step C:

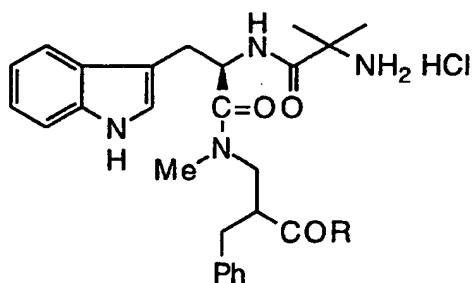
Prepared from the intermediate from the previous step (24 mg) by the procedure described in Example 22, Step C to give the coupling product. The residue was purified (chromatotron, methylene chloride/ methanol=20/1) to give the desired compound (17 mg, 48%). Diastereomers separated during purification where applicable.

Step D:

Prepared from the intermediate from the previous step (17 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (15 mg).

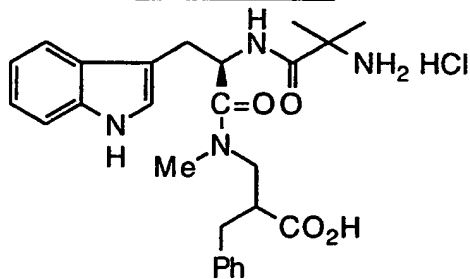
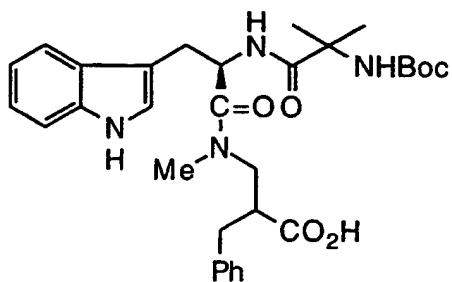
FAB-MS: 492.0 (M+1)

- 91 -

TABLE III

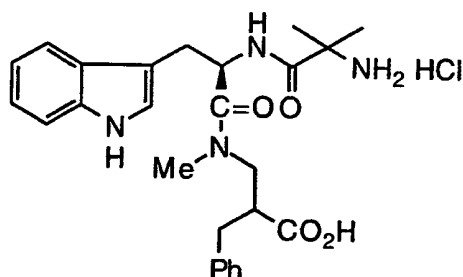
The additional final products shown in table were prepared to the above established procedure (with different amines) as exemplified in Example 26.

		<u>R</u>	<u>FAB-MS (M+1)</u>
1	d1+d2	morpholine	534.1
2	d1	N-methyl piperazine	547.3
3	d2	N-methyl piperazine	547.3
4	d1+d2	dimethyl amine	492.1

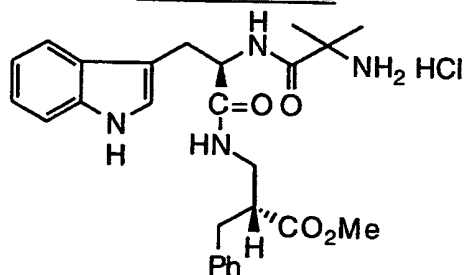
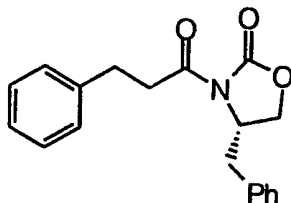
EXAMPLE 27Step A:

- 92 -

To a stirred solution of the intermediate from Example 25, Step B (110 mg) in 5 mL of methanol was added 5 mL of 6N sodium hydroxide. This reaction was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was diluted with water and acidified with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired compound (64 mg, 60%).

Step B:

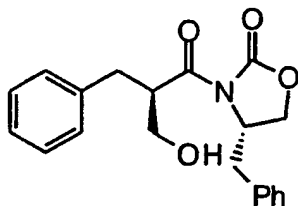
Prepared from the intermediate obtained from the previous step (20 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (13mg). FAB-MS: 465.0 (M+1)

EXAMPLE 28Step A:

- 93 -

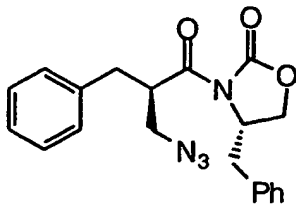
To a solution of (4S)-benzyl oxazolidinone (1.77 g) in THF (40 ml) was added n-butyllithium (1.6 M, 8 ml) at -78°C. After 30 minutes, to the reaction mixture was added hydrocinnamoyl chloride (1 eq) and the mixture was warmed to room temperature for 5 minutes. The mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by chromatatron (hexanes/ethyl acetate=5/1) to give the desired product 2.06g.

10 Step B:



A solution of the intermediate (1.24 g) obtained from Step A in methylene chloride (20 ml) was cooled to 0°C and treated dropwise with TiCl<sub>4</sub> (0.46 ml). After 5 minutes, diisopropylethylamine (0.74 ml) was added slowly and the resultant deep red solution was stirred at 0°C for 1 hour. To this deep red solution was added trioxane (400 mg) in methylene chloride (4 ml) and the resulting mixture was stirred for additional 5 minutes. Then, another portion of TiCl<sub>4</sub> (0.46 ml) was added. After stirring 2.5 hour at 0°C, this clear solution was quenched with saturated aqueous ammonium chloride. This mixture was extracted with methylene chloride, washed with sodium bicarbonate, brine and dried over sodium sulfate. Concentration and purification (hexanes/ethyl acetate=4/1) gave the desired product 0.79 g.

30 Step C:

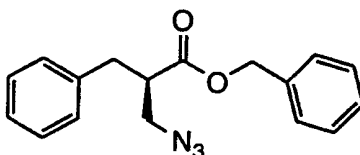


- 94 -

To a solution of the intermediate (0.7 g) obtained from Step B in THF (20 ml) was added triphenylphosphine (0.595 g) and diethylazodicarboxylate (0.357 ml) and then added diphenylphosphorylazide (0.488 ml) was added slowly. After stirring for 60 hours, the mixture was concentrated. The resulting residue was filtered through a plug of silica gel (100% ether) and concentrated. The material was purified by chromatatron (hexanes/ethyl acetate=10/1) to give the desired product (189 mg) and unreacted starting material (463 mg).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.21 (m, 10 H), 4.50 (m, 1 H), 4.35 (m, 1 H), 4.06 (dd, 9 Hz, 3 Hz, 1H), 3.92 (t, 8 Hz, 1 H), 3.68 (dd, 12 Hz, 8 Hz, 1 H), 3.42 (dd, 12 Hz, 5 Hz, 1 H), 3.22 (dd, 13 Hz, 3 Hz, 1H), 2.95 (dd, 13 Hz, 7 Hz, 1H), 2.78 (t, 9 Hz, 1H), 2.74 (t, 9 Hz, 1H). FAB-MS: 365.2 (M+1).

Step D:



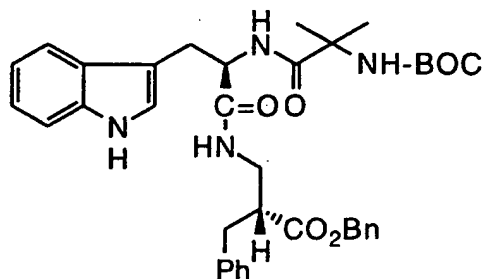
To a solution of benzyl alcohol (0.16 ml) in THF (5 ml) was added n-butyllithium (0.65 ml, 1.6 M) at 0°C. After stirring 10 minutes, the intermediate (189 mg) obtained from Step C in THF (2 ml) was added to the reaction mixture. The resulting solution was stirred for an hour at 0°C and quenched with 1 N HCl. The mixture was extracted with ether, washed with brine and dried over MgSO<sub>4</sub>. Concentration and purification (PLC, hexanes/ethyl acetate=20/1) to give the desired product (87 mg).

Step E:



- 95 -

5

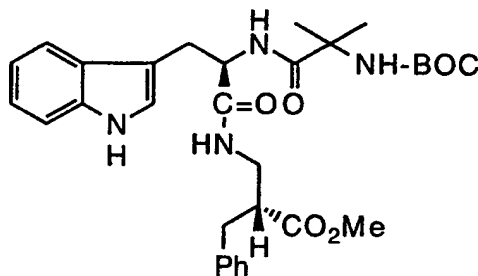


10

To a solution of the intermediate (87 mg) obtained from Step D in methanol was added Raney nickel and under 1 atmosphere of hydrogen for 2 hours. The mixture was filtered through Celite and the filtrate was concentrated. The residue was coupled to the Intermediate 1 by the procedure described in Example 1, Step B (without NMM) to give desired compound (101 mg).

15 Step F:

20

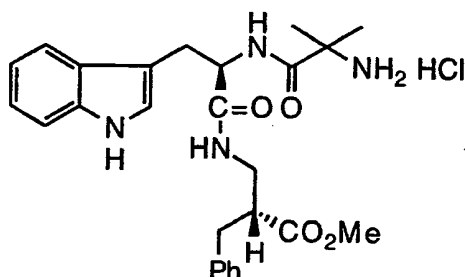


25

To a solution of the intermediate (101 mg) obtained from Step E in methanol was added Pd(OH)<sub>2</sub> and hydrogenated under hydrogen (1 atmosphere) for an hour. The mixture was filtered through Celite. The filtrate was concentrated to give corresponding acid (88 mg). The acid (17 mg) in ether was added diazomethane (prepared from N-methyl N-nitroso urea) at 0°C until the solution turned yellow. The yellowish solution was stirred for a couple of hours at room temperature and concentrated. The residue was purified by PLC (hexanes/ethyl acetate=1/2) to give the desired product (11 mg).

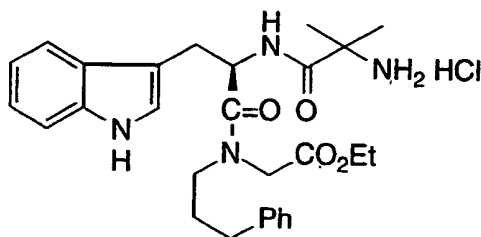
30

- 96 -

Step G:

Prepared from the intermediate obtained from Step F and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (9 mg).

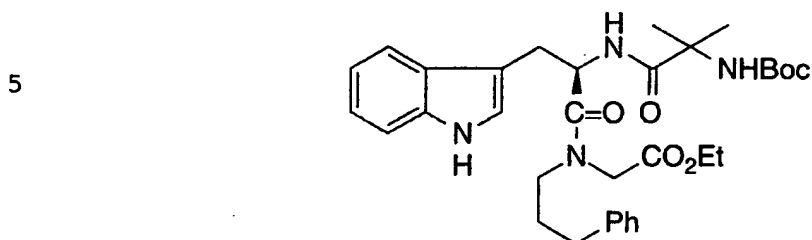
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): 7.62 (d, 8 Hz, 1 H), 7.31 (d, 8 Hz, 1 H), 7.26-7.06 (m, 7 H), 7.01 (t, 7 Hz), 4.70 (dd, 9 Hz, 2 Hz, 1 H), 3.56 (s, 3H), 3.39-3.24 (m, 3 H), 3.10 (dd, 14 Hz, 9 Hz, 1 H), 2.85 (m, 1 H), 2.74 (m, 2 H), 1.54 (s, 3 H), 1.32 (s, 3 H).  
FAB-MS: 465.1 (M+1).

EXAMPLE 29Step A: N-(3-phenyl-1-propyl)glycine ethyl ester

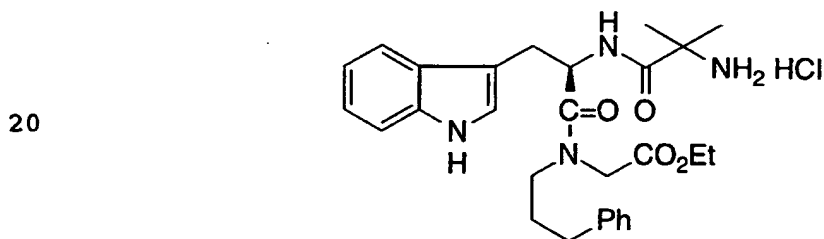
To a stirred solution of 3-phenyl-1-propylamine (5 mL, 35.2 mmol) in THF (20 mL), was added ethyl bromoacetate (3.9 mL, 35.2 mmol) and diisopropyl ethyl amine (6.13 mL). The reaction was stirred at room temperature overnight. The solid formed was filtered off and the solution was evaporated and purified by flash column to yield the desired material (2 g)

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ (ppM) 7.28-7.13 (m, 5 H), 4.13 (q, J=7.2 Hz, 3 H), 3.37 (s, 2 H), 2.68-2.60 (m, 4 H), 1.88-1.76 (m, 2 H), 1.25 (t, J=7.2 Hz, 3 H).

- 97 -

Step B:

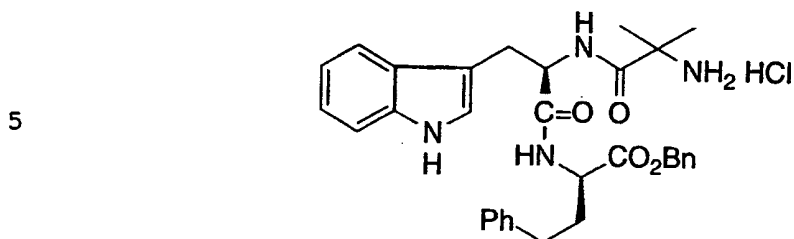
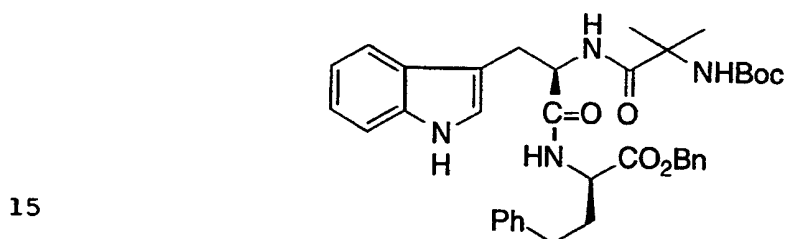
10 Prepared by the procedure described in Example 1, Step B from the intermediate from the previous step (170 mg), Intermediate 1 (200 mg, 0.514 mmol), HOBT (68 mg.), and EDC (200 mg). Product: 254.8 mg. FAB-MS calc. for C<sub>33</sub>H<sub>44</sub>N<sub>4</sub>O<sub>6</sub>: 592; found: 593 (M+H).

Step C:

25 Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (228.8 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 30 minutes. Product: 210 mg. FAB-MS calc. for C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub>: 492; found: 493 (M+H).

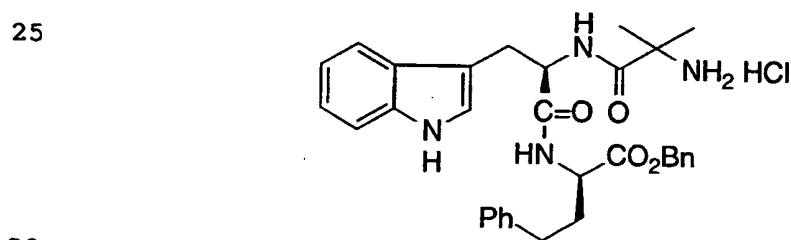
30

- 98 -

EXAMPLE 30Step A:

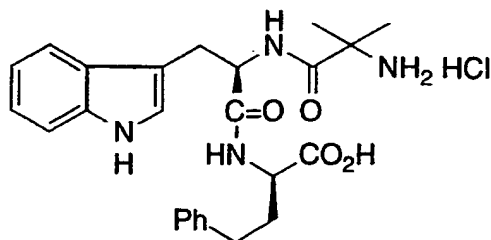
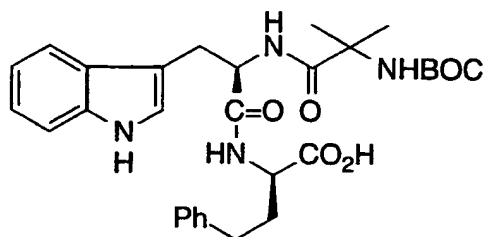
Prepared by the procedure described in Example 1, Step B from D-HomoPhe benzyl ester (1.38 g, 5.13 mmol), Intermediate 1 (2 g, 5.13 mmol), HOBT (694 mg), and EDC (1.53 g). Product: 2.90 g, (88%).

FAB-MS calc. for C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>6</sub>: 640; found: 641 (M+H).

Step B:

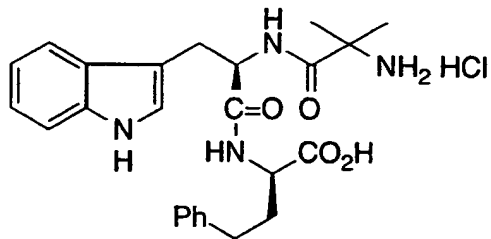
Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (106 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 1 hour. Product: 94.5 mg. FAB-MS calc. for C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub>: 540; found: 541 (M+H).

- 99 -

EXAMPLE 31Step A:

A solution of the material from Step A (2.74 g) of the previous example in 20 mL of ethanol was stirred at RT under a H<sub>2</sub> balloon for 20 minutes in the presence of 10% palladium on carbon (150 mg). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a foam (2.19 g, 93%).

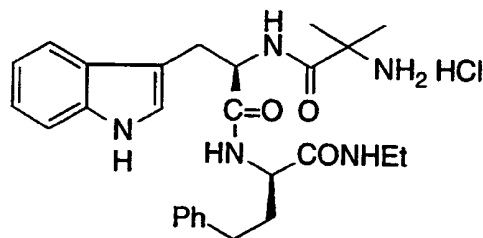
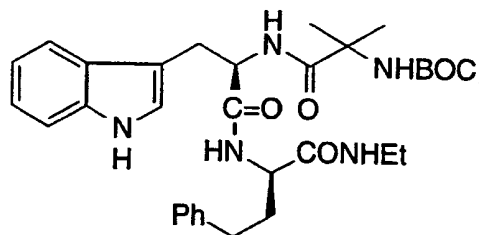
FAB-MS calc. for C<sub>30</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub>: 550 ; Found 551 (M+H)

Step B:

- 100 -

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (150 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 15 minutes. Product: 128 mg (96.5%).

- 5 FAB-MS calc. for  $C_{25}H_{30}N_4O_4$ : 450 ; Found 451 (M+H)  
 $^1H$ NMR (400 MHz,  $CD_3OD$ ):  $\delta$  (ppM) 8.50 (d, J=8 Hz, 1 H), 7.69 (d, J=8 Hz, 1 H), 7.31-7.00 (m, 8 H), 4.89-4.85 (m, 1 H), 4.39-4.35 (m, 1 H), 3.38 (dd, J=4, 14 Hz, 1 H), 3.16 (dd, J=10, 14 Hz, 1 H), 2.72-2.64 (m, 2 H), 2.21-2.12 (m, 1 H), 2.08-1.98 (m, 1 H), 1.53 (s, 3 H), 1.27 (s, 3 H).

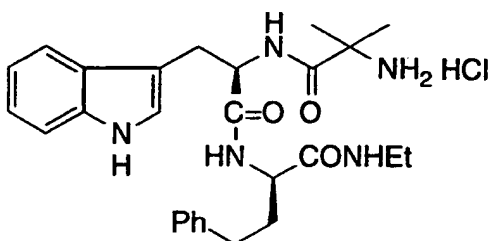
EXAMPLE 3220 Step A:

- 25 Prepared by the procedure described in Example 1, Step B from the intermediate from Step A of the previous example (150 mg, 0.272mmol), ethyl amine hydrochloride (25 mg, 0.544 mmol), HOBT (37 mg), N-methyl morpholine(0.06 mL; 0.544 mmol), and EDC (100 mg). Product: 139 mg. FAB-MS calc. for  $C_{32}H_{43}N_5O_5$ : 577 ; Found 578 (M+H)

- 101 -

Step B:

5



Prepared by the procedure described in Example 1, Step  
10 B from the intermediate from previous step ( 125 mg) and HCl gas in  
ethyl acetate (3 mL) at 0°C. Reaction time: 15 minutes. Product: 90.9  
mg (82%).

FAB-MS calc. for C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>3</sub>: 477 ; Found 478 (M+H)

<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ (ppM) 8.19 (d, J=7.5 Hz, 1 H), 7.66-  
15 7.00 (m, 10 H), 4.85-4.79 (m, 1 H), 4.29-4.26 (m, 1 H), 3.57 (dd, J=6,  
14 Hz, 1 H), 3.16 (dd, J=9, 14 Hz, 1 H), 3.15-3.08 (m, 2 H), 2.68-2.55  
(2 m, 2 H), 2.10-1.98 (m, 1 H), 1.95-1.86 (m, 1 H), 1.55 (s, 3 H), 1.34  
(s, 3 H), 1.05 (t, J=7.2 Hz).

20

25

30

- 102 -

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be  
5 made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the  
10 specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance  
15 with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

20

25

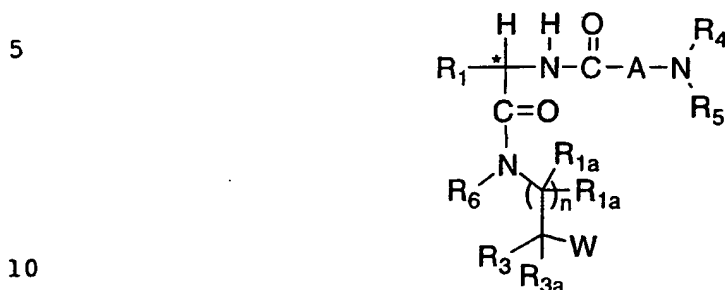
30



- 103 -

WHAT IS CLAIMED IS:

1. A compound of the formula



Formula I

wherein:

R<sub>1</sub> is selected from the group consisting of:

- 15 C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, (C<sub>1</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, and (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>5</sub> alkyl)-, where K is O, S(O)<sub>m</sub>, N(R<sub>2</sub>)C(O), C(O)N(R<sub>2</sub>), OC(O), C(O)O, -CR<sub>2</sub>=CR<sub>2</sub>-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindolyl,
- 20 pyridyl, benzothieryl, benzofuranyl, thiazolyl, and benzimidazolyl, and where R<sub>2</sub> and alkyl may be further substituted by 1 to 9 halogen, S(O)<sub>m</sub>R<sub>2a</sub>, 1 to 3 of OR<sub>2a</sub> or C(O)OR<sub>2a</sub>, and aryl may be further substituted by 1 to 3 of C<sub>1</sub>-C<sub>6</sub> alkyl, 1 to 3 of halogen, 1 to 2 of OR<sub>2</sub>, methylenedioxy, -N(R<sub>2</sub>)(R<sub>2</sub>), -S(O)<sub>m</sub>R<sub>2</sub>, 1 to 2 of -CF<sub>3</sub>, -OCF<sub>3</sub>,
- 25 -C(O)H, nitro, -N(R<sub>2</sub>)C(O)(R<sub>2</sub>), -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -1H-tetrazol-5-yl, -SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)SO<sub>2</sub> phenyl, or -N(R<sub>2</sub>)SO<sub>2</sub>R<sub>2</sub>; R<sub>1a</sub> is independently hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and

30 C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one atom, they may be optionally joined to form a C<sub>3</sub>-C<sub>8</sub> cyclic ring, optionally including oxygen, sulfur, SO<sub>2</sub> or NR<sub>2a</sub>;

R<sub>2a</sub> is hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by hydroxyl;

- 104 -

R<sub>3</sub> is independently selected from the group consisting of:  
 hydrogen, -C<sub>1</sub>-C<sub>10</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, -(CH<sub>2</sub>)<sub>r</sub>naphthyl,  
 -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>8</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>8</sub>),  
 (C<sub>1</sub>-C<sub>6</sub> alkyl)-K-(C<sub>1</sub>-C<sub>4</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>5</sub> alkyl)-K-(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
 5 -(CH<sub>2</sub>)<sub>r</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl,  
 where K is O or S(O)<sub>m</sub>, and where heteroaryl is selected from: pyridyl,  
 indolyl, imidazolyl, quinolinyl, benzothiophenyl, benzofuranyl, indanyl,  
 thiazolyl, benzimidazolyl, and azaindolyl, and  
 where the phenyl, naphthyl and heteroaryl may be substituted by:  
 10 C<sub>1</sub>-C<sub>6</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>9</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, -C(O)H,  
 -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>2</sub>)(R<sub>9</sub>), -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>2</sub>)C(O)R<sub>9</sub>,  
 -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>9</sub>), -(CH<sub>2</sub>)<sub>r</sub>N(R<sub>6</sub>)C(O)N(R<sub>2</sub>)(R<sub>9</sub>), or -(CH<sub>2</sub>)<sub>r</sub>(R<sub>9</sub>);

R<sub>3a</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

15

R<sub>4</sub> and R<sub>5</sub> are independently selected from:  
 hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the  
 substituents are selected from: 1 to 5 halogen, 1 to 3 of hydroxy, 1 to 3  
 of C<sub>1</sub>-C<sub>10</sub> alkanoyloxy, 1 to 3 of C<sub>1</sub>-C<sub>6</sub> alkoxy, phenyl, phenoxy,  
 20 2-furyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, and S(O)<sub>m</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl); or R<sub>4</sub> and  
 R<sub>5</sub> can be taken together to form -(CH<sub>2</sub>)<sub>d</sub>L<sub>a</sub>(CH<sub>2</sub>)<sub>e</sub>- where L<sub>a</sub> is  
 C(R<sub>2</sub>)<sub>2</sub>, O, S(O)<sub>m</sub> or N(R<sub>2a</sub>), d and e are independently 1 to 3 ;

R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

25

R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl,  
 phenyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from:  
 imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR<sub>2</sub>, S(O)<sub>m</sub>R<sub>2</sub>,  
 C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, N(R<sub>2</sub>)(R<sub>2</sub>), and  
 30 C(O)N(R<sub>2</sub>)(R<sub>2</sub>); or R<sub>7</sub> and R<sub>7a</sub> can independently be joined to one or  
 both of R<sub>4</sub> and R<sub>5</sub> groups to form an alkylene bridge between the  
 terminal nitrogen and the alkyl portion of the R<sub>7</sub> or R<sub>7a</sub> groups, wherein  
 the bridge contains 1 to 5 carbons atoms; or R<sub>7</sub> and R<sub>7a</sub> can be joined to  
 one another to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

- 105 -

R<sub>8</sub> is selected from the group consisting of:

hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl groups may be substituted by a substituent selected from the group consisting of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
 5 and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, naphthyl, indolyl, quinolinyl, benzothiopheneyl, benzofuranyl, azaindolyl, benzimidazolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen,  
 1 to 2 of C<sub>1</sub>-C<sub>3</sub> alkyl, -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), or -1H-tetrazol-5-yl;

R<sub>9</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or (CH<sub>2</sub>)<sub>v</sub>aryl, wherein the alkyl and (CH<sub>2</sub>)<sub>v</sub> groups may be optionally substituted by 1 to 2 of -O(R<sub>2</sub>), -S(O)<sub>m</sub>R<sub>2</sub>, -N(R<sub>2</sub>)(R<sub>2</sub>), 1H-tetrazol-5-yl, -C(O)OR<sub>2</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), or -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), and where aryl is selected  
 15 from: phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, and benzimidazol-2-yl, triazolinone-yl, and where the aryl is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, amino, hydroxyl, or -C(O)O(R<sub>2</sub>);

20 A is:



25 where x and y are independently 0, 1, 2 or 3;

W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)NH-SO<sub>2</sub>(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>), -CH<sub>2</sub>N(R<sub>2</sub>)C(O)R<sub>8</sub>, -CH<sub>2</sub>N(R<sub>2</sub>)C(O)(R<sub>8</sub>), -(CH<sub>2</sub>)<sub>r</sub>OR<sub>2</sub>,  
 30 -CH(OH)R<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>R<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>N(R<sub>2</sub>)(R<sub>2</sub>), 1H-tetrazol-5-yl, 5-amino-1,2,4-oxadiazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

- 106 -

m is 0, 1, or 2;  
n is 0 or 1;  
r is 0, 1, 2, or 3;  
v is 0, 1, or 2 ;

5 and pharmaceutically acceptable salts and individual diastereomers thereof.

2. The compound of Claim 1 wherein:

10 R<sub>1</sub> is selected from the group consisting of:  
C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
(C<sub>1</sub>-C<sub>4</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, aryl(C<sub>0</sub>-C<sub>2</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-,  
and (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)(C<sub>0</sub>-C<sub>2</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, where K is O,  
S(O)<sub>m</sub>, OC(O), or C(O)O, where the alkyl groups may be further  
15 substituted by 1 to 7 halogen, S(O)<sub>m</sub>R<sub>2a</sub>, 1 to 3 of OR<sub>2a</sub> or C(O)OR<sub>2a</sub>,  
and where aryl is selected from: phenyl, naphthyl, indolyl, pyridyl,  
benzimidazolyl, azaindolyl, benzothienyl, and benzofuranyl, and where  
the aryl may be further substituted by 1 to 2 of C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of  
halogen, -C(O)H, 1 to 2 of -OR<sub>2</sub>, -S(O)<sub>m</sub>R<sub>2</sub>, or -C(O)OR<sub>2</sub>;  
20 R<sub>1a</sub> is independently hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and  
C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one  
atom they may be optionally joined to form a C<sub>4</sub>-C<sub>7</sub> cyclic ring  
25 optionally including oxygen, sulfur or NR<sub>2a</sub>;  
R<sub>2a</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>3</sub> is independently selected from the group consisting of:  
hydrogen, -C<sub>1</sub>-C<sub>8</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, -(CH<sub>2</sub>)<sub>r</sub>naphthyl,  
30 and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl, where heteroaryl is selected from: pyridyl,  
indolyl, quinolinyl, benzothiophenyl, benzofuranyl, thiazolyl,  
benzimidazolyl, and azaindolyl, and where the phenyl, naphthyl and  
heteroaryl may be substituted by: C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of halogen, 1 to 2

- 107 -

of -OR<sub>2</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>2</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
-(CH<sub>2</sub>)<sub>r</sub>N(R<sub>6</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), or -(CH<sub>2</sub>)<sub>r</sub> (R<sub>9</sub>);

R<sub>3a</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

5

R<sub>4</sub> and R<sub>5</sub> are independently selected from: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from: 1 to 5 of halogen, 1 to 3 of hydroxyl, S(O)<sub>m</sub> (C<sub>1</sub>-C<sub>6</sub> alkyl), and phenyl;

10 R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl, phenyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from: imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR<sub>2</sub>, S(O)<sub>m</sub>R<sub>2</sub>,

15 C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, N(R<sub>2</sub>)(R<sub>2</sub>), and C(O)N(R<sub>2</sub>)(R<sub>2</sub>); or R<sub>7</sub> and R<sub>7a</sub> can independently be joined to one or both of R<sub>4</sub> and R<sub>5</sub> groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R<sub>7</sub> or R<sub>7a</sub> groups, wherein the bridge contains 1 to 5 carbons atoms; or R<sub>7</sub> and R<sub>7a</sub> can be joined to  
20 one another to form a C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

R<sub>8</sub> is selected from the group consisting of:

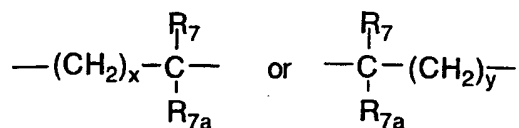
hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl groups may be substituted by a substituent selected from the group  
25 consisting of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, indolyl, azaindolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen, or 1 to 2 of C<sub>1</sub>-C<sub>3</sub> alkyl;

30

R<sub>9</sub> is (CH<sub>2</sub>)<sub>v</sub>aryl, where aryl is selected from: phenyl, pyridyl, 1H-tetrazol-5-yl, or oxadiazolyl, and where the aryl is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, amino, hydroxyl, or -C(O)O(R<sub>2</sub>);

- 108 -

A is:



5

where x and y are independently 0, 1, 2 or 3;

W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>,  
 -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>), 1H-tetrazol-5-yl,  
 10 3-amino-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl,  
 5-amino-1,2,4-oxadiazol-3-yl, and 5-methyl-1,2,4-oxadiazol-3-yl;

m is 0, 1, or 2;

n is 0 or 1;

15 r is 0, 1, 2, or 3;

v is 0, 1, or 2 ;

and pharmaceutically acceptable salts and individual diastereomers thereof.

20

3. The compound of Claim 1 wherein:

R<sub>1</sub> is selected from the group consisting of: C<sub>1</sub>-C<sub>10</sub> alkyl,  
 aryl (C<sub>1</sub>-C<sub>3</sub> alkyl)-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-, and  
 25 aryl (C<sub>0</sub>-C<sub>1</sub> alkyl)-K-(C<sub>1</sub>-C<sub>2</sub> alkyl)-, where K is O or S(O)<sub>m</sub> and aryl is  
 selected from: phenyl, pyridyl, naphthyl, indolyl, azaindolyl, and  
 benzofuranyl and where the aryl may be further substituted by 1 to 2 of  
 C<sub>1</sub>-C<sub>4</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>2</sub>, -S(O)<sub>m</sub> R<sub>2</sub>, or  
 -C(O)OR<sub>2</sub>;

30

R<sub>1a</sub> is independently hydrogen or C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sub>2</sub> is selected from the group consisting of: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and  
 C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and where two C<sub>1</sub>-C<sub>6</sub> alkyl groups are present on one

- 109 -

atom they may be optionally joined to form a C5-C7 cyclic ring optionally including oxygen, sulfur or NR<sub>2a</sub>;

R<sub>2a</sub> is hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

- 5 R<sub>3</sub> is independently selected from the group consisting of:  
hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>r</sub>phenyl, and -(CH<sub>2</sub>)<sub>r</sub>heteroaryl, where  
heteroaryl is selected from: pyridyl, thiazolyl, indolyl, quinolinyl,  
benzofuranyl, and azaindolyl, and where the phenyl and heteroaryl may  
be substituted by: C<sub>1</sub>-C<sub>3</sub> alkyl, 1 to 2 of halogen, 1 to 2 of -OR<sub>2</sub>,  
10 -(CH<sub>2</sub>)<sub>r</sub>C(O)OR<sub>2</sub>, -(CH<sub>2</sub>)<sub>r</sub>C(O)N(R<sub>2</sub>)(R<sub>2</sub>),  
-(CH<sub>2</sub>)<sub>r</sub>N(R<sub>6</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), or -(CH<sub>2</sub>)<sub>r</sub> (R<sub>9</sub>);

R<sub>3a</sub> is hydrogen or C<sub>1</sub> alkyl;

- 15 R<sub>4</sub> and R<sub>5</sub> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or substituted  
C<sub>1</sub>-C<sub>3</sub> alkyl where the substituents are selected from: 1 to 5 of halogen,  
1 to 3 of hydroxyl, S(O)<sub>m</sub> (C<sub>1</sub>-C<sub>6</sub> alkyl), and phenyl;

R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

- 20 R<sub>7</sub> and R<sub>7a</sub> are independently hydrogen, C<sub>1</sub>-C<sub>2</sub> alkyl, phenyl, substituted  
C<sub>1</sub>-C<sub>6</sub> alkyl where the substituents are selected from: imidazolyl,  
phenyl, indolyl, p-hydroxyphenyl, -OR<sub>2</sub>, and -S(O)<sub>m</sub>R<sub>2</sub>, or R<sub>7</sub> and R<sub>7a</sub>  
can independently be joined to one of R<sub>4</sub> and R<sub>5</sub> groups to form an  
25 alkylene bridge between the terminal nitrogen and the alkyl portion of the  
R<sub>7</sub> or R<sub>7a</sub> groups to form a 5 or 6 membered ring; or R<sub>7</sub> and R<sub>7a</sub> can be  
joined to one another to form a C<sub>3</sub> cycloalkyl;

R<sub>8</sub> is selected from the group consisting of:

- 30 hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and aryl-C<sub>1</sub>-C<sub>2</sub> alkyl, where the alkyl groups  
may be substituted by a substituent selected from the group consisting  
of: -OR<sub>2</sub>, -C(O)OR<sub>2</sub>, -CON(R<sub>2</sub>)(R<sub>2</sub>), -N(R<sub>2</sub>)C(O)N(R<sub>2</sub>)(R<sub>2</sub>), and

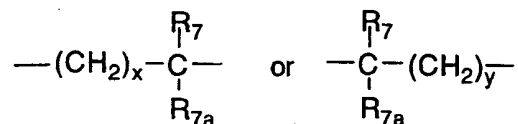
- 110 -

1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, indolyl, 7-azaindolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR<sub>2</sub>, 1 to 2 of halogen, or 1 to 2 of C<sub>1</sub>-C<sub>3</sub> alkyl;

5

R<sub>9</sub> is (CH<sub>2</sub>)<sub>v</sub>aryl, where aryl is selected from: 1H-tetrazol-5-yl, and oxadiazolyl, and where the aryl is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, amino, or hydroxyl;

10 A is:



15 where x and y are independently 0 or 1;

W is selected from the group consisting of: hydrogen, -C(O)OR<sub>8</sub>, -C(O)N(R<sub>2</sub>)(R<sub>2</sub>), -C(O)N(R<sub>2</sub>)(R<sub>8</sub>), 1H-tetrazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

20

m is 0, 1, or 2;  
n is 0 or 1;  
r is 0, 1, 2, or 3;  
v is 0, 1, or 2 ;

25

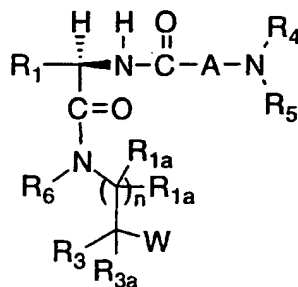
and pharmaceutically acceptable salts and individual diastereomers thereof.

30



- 111 -

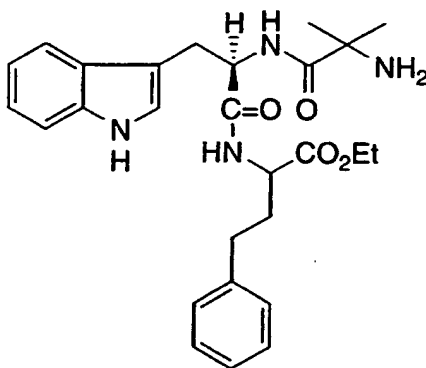
4. The stereospecifically defined compound of Claim 1  
of the formula:



Formula Ia

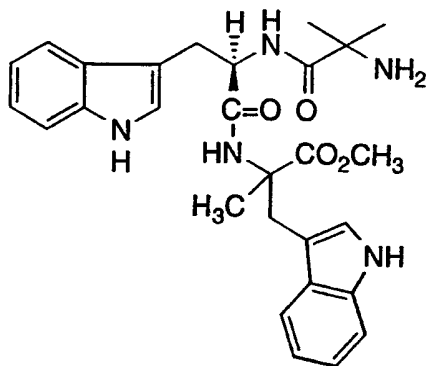
where R<sub>1</sub>, R<sub>3</sub>, R<sub>3a</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, A, W and n are as defined in Claim 1.

5. A compound which is selected from the group  
consisting of:

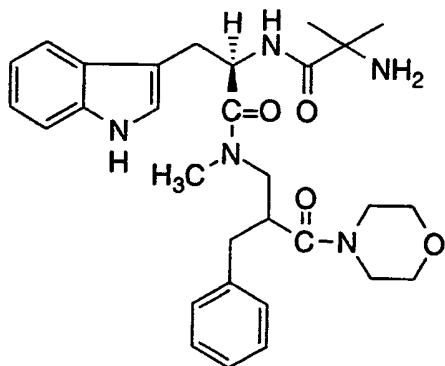


- 112 -

5

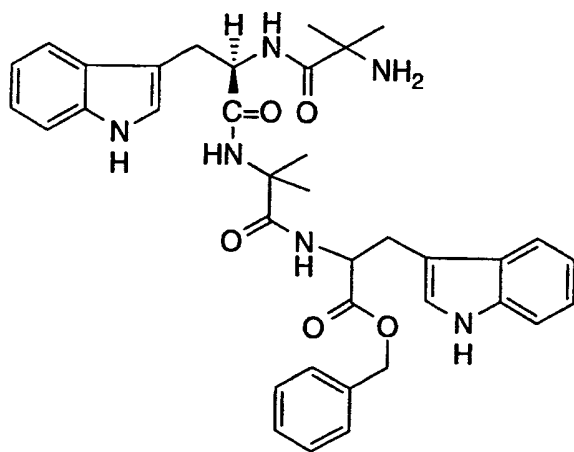


10



15

20

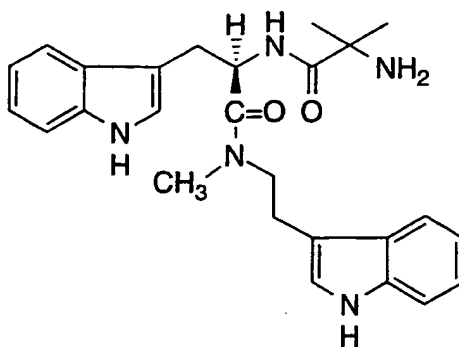


25

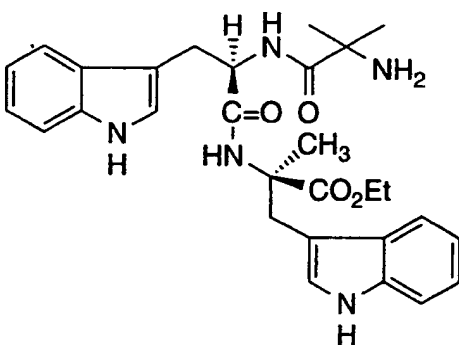
30

- 113 -

5

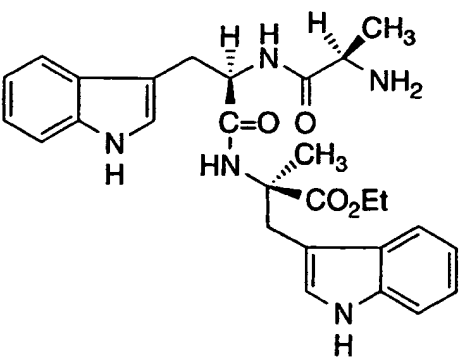


10



15

20

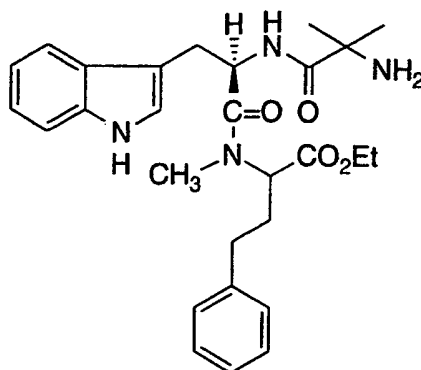


25

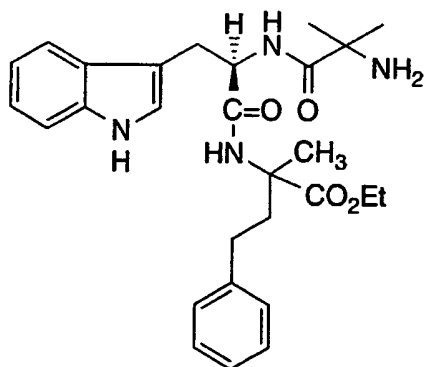
30

- 114 -

5

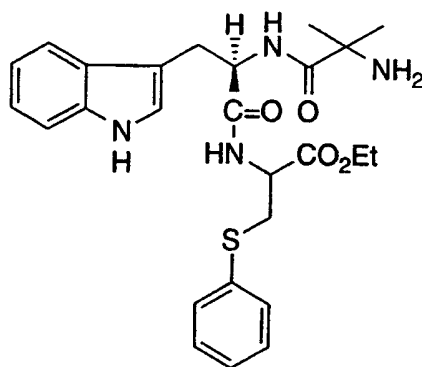


10



15

20



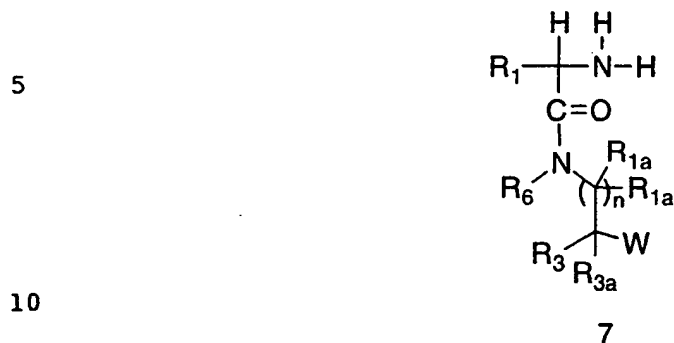
25

30

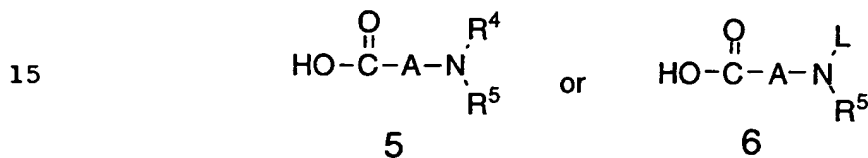
and their pharmaceutically acceptable salts and individual diastereomers thereof, where not otherwise specified.

- 115 -

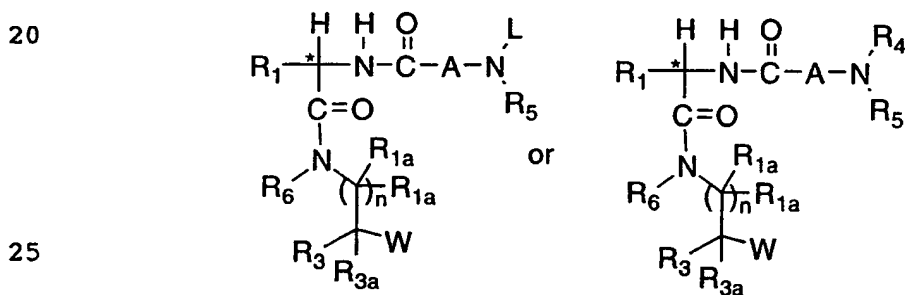
6. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:



with a compound of the formula:



to give a compound of the formula:

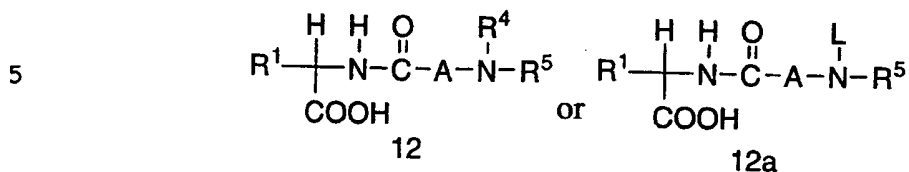


where R<sub>1</sub>, R<sub>3</sub>, R<sub>3a</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, A, W, and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

30

- 116 -

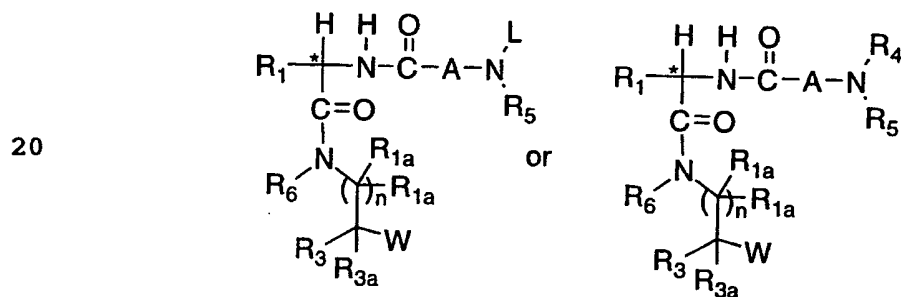
7. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:



with a compound of the formula:



to give a compound of the formula:



where R<sub>1</sub>, R<sub>3</sub>, R<sub>3a</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, A, W, and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

- 117 -

8. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

5

9. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an additional growth hormone secretagogue.

10

10. The composition of Claim 9 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing peptide GHRP-6; growth hormone releasing peptide GHRP-2; growth hormone releasing peptide GHRP-1; B-HT920; growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1 and IGF-2.

15

11. A composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and a compound of Claim 1.

20

12. The composition of Claim 11 wherein the bisphosphonate compound is alendronate.

25

13. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

14. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of a compound of Claim 1.

30

- 118 -

15. A method of treating or preventing a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth  
5 hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

10

16. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and a compound of Claim 1.

15

17. The method of Claim 16 wherein the bisphosphonate compound is alendronate.

20

25

30



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/13596

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 209/20, 403/12; A61K 31/405

US CL : 548/455, 495; 514/414, 419

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/455, 495; 514/414, 419

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE STRUCTURE SEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,658,038 (TAMIR ET AL) 14 April 1987, see entire document.	1-5
A	US, A, 4,522,824 (WAGNON ET AL) 11 June 1985, see entire document.	1-5
A,P	US, A, 5,324,737 (D'AMBRA ET AL) 28 June 1994, see entire document.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

<p>* Special categories of cited documents:</p>	
*A* document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*E* earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*O* document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  
15 MARCH 1995

Date of mailing of the international search report

28 MAR 1995

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

DAVID B. SPRINGER

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235

**THIS PAGE BLANK (USPTO)**

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

**THIS PAGE BLANK (USPTO)**